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Psychological distress in patients with neurodegenerative diseases: towards an ever more complex vision of the person and the care.

PhD Thesis

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1. Reference models

My research area is clinical psychology. More in detail, my studies focused on individuals facing impacting medical diseases to which they are called to adapt. Thus, the person and his subjective reactions to objective clinical conditions has been at the center of my research observations.

In this sense, I consider psychological distress as different types of psychological symptoms that can arise when the individual faces difficulties in the adaptation process to the disease.

Therefore, the final objective of my research was to discover why, when, and how these symptoms arise during the illness course. And the starting clinical hypothesis of my studies was that symptoms manifest always for some reason; in other words, the person's subjective system of reactions, meanings, and internal/external functioning manifests symptoms of distress every time he struggles to integrate and accept new disturbing health status-related information.

For these reasons, the bio-psycho-social model and the constructivism have been my reference models to understand what an individual with an organic disease lives and feels, and they guided me in my research.

1.1 The biopsychosocial model

According to the biopsychosocial model, health and illness are modulated not only by biological aspects (e.g., infective, hormonal, metabolic, immune), but also by psychological components (e.g., anxious, and depressive symptoms, chronic distress, personality traits) and social conditions (e.g., relationships, external

resources, and the environment) (Papadimitriou et al., 2017; Karanamuni et al., 2020).

The overlaps between psyche and soma and the interconnections between the central nervous system, the endocrine system and immune system are the mechanisms through which the patient subjectively reacts and adapts to the medical illness. In this sense, the psychic aspects can influence the occurrence and course of the medical illnesses. The psycho-neuro-endo-immune interactions mediate the reciprocal influences between psyche and soma and play a significant role with respect to illness (Torta & Mussa, 2021).

In 1977, George Engel finally provided value to these aspects, promoting a more comprehensive approach to patients which should also include the emotional and social factors, i.e., the biopsychosocial model. The critical point of the biomedical reductionism is the risk of considering the disease without considering the person who is affected by that disease. In the care process, it is essential to know both the disease and the patient.

Consequently, it is of fundamental relevance the concept of "patient centricity" in the care process. The patient and its subjective reaction and adaptation to the disease might be part of the assessment and intervention. Patient centricity means openness and continuous communication among patients, healthcare operators and caregivers, with the aim to share knowledge and choices in a context of reciprocal respect and empathy (McDonald et al., 2019). The care process not only includes the illness treatment, but it also comprehends the care of patient's quality of life, the satisfaction of his needs, and the intervention on the psycho-social aspects of his illness experience.

Some extracts of a published manual contribution on the psychosocial aspects of pain are reported in the following paragraph to represent, as a paradigmatic example,

the way in which I theorized the medical conditions for my PhD Project, i.e., integrating their objective presentation with patients' subjective experiences of them. The extracts are in Italian language because the manual contribution was published in Italian language.

1.2 Manual contribution n. 1

Aspetti bio-psico-sociali del dolore.

Botto R., Torta R.

Published on: Grassi L. Cure psicosociali in medicina palliativa. Poletto Ed., 2021.

[…] Storicamente, il concetto di dolore è stato inteso come l'esito di una relazione diretta tra una stimolazione o un danno tissutale e l'outcome dolorifico conseguente, ritenendo gli aspetti psicologici come secondari e scarsamente rilevanti ai fini della comprensione e trattamento del dolore "reale" e "organico". Si iniziò successivamente a parlare di dolore funzionale o psicogeno, quando l'evidenza di un dolore riferito non era provata da una condizione patologica oggettivamente osservabile, assumendo, dunque, che i processi psicologici potessero avere un ruolo causale sul dolore. Attualmente, è ormai da diversi decenni che la letteratura scientifica dimostra che, quando si parla di dolore, si fa riferimento a un fenomeno psico- sociale complesso, qualunque sia la sua entità: l'esperienza del dolore è, infatti, soggettiva e comprensiva di costrutti fisici, biomedici, cognitivi, affettivi e

comportamentali, i quali sono essenziali per caratterizzarla e per comprenderne gli effetti e le conseguenze. A questo proposito, l'Associazione internazionale per lo studio del dolore (International Association for the Study of Pain IASP) definisce il dolore come un'esperienza sensoriale ed emozionale spiacevole, associata a danno tissutale, in atto o potenziale, o descritta in termini di danno, IASP specifica, inoltre, che il dolore si può intendere come esperienza individuale e soggettiva, a cui convergono componenti puramente sensoriali, relative al trasferimento dello stimolo doloroso dalla periferia alle strutture centrali, e componenti esperienziali e affettive, che modulano in maniera importante quanto percepito. È evidente, dunque, che l'esperienza algica sia da intendersi come multidimensionale e differenti fattori psico-sociali possono influenzarla, sia in termini d'impatto sulla qualità di vita della persona, sia di richiesta di assistenza e di aderenza ai trattamenti della stessa.

[…] Una dimensione dolorifica può dare origine a una condizione di inattività, in cui l'evitamento delle attività, che si teme possano esacerbare o mantenere il dolore, contribuisce a rendere più intenso e prolungato il dolore stesso e riduce il benessere funzionale della persona. Al contempo, all'inattività può sovrapporsi un quadro di iperattività, dato dal distress emozionale e/o dalla ruminazione cognitiva, che genera alterazioni autonomiche dell'organismo, le quali, a loro volta, amplificano la percezione dolorifica: per esempio, nel caso di dolore temporomandibolare, ansia e stress possono generare una prolungata contrazione dei muscoli facciali, che mantiene e alimenta il dolore il quale, a sua volta, favorisce il perdurare dello stato ansioso, modificando il tono muscolare e contribuendo al mantenimento dei sintomi.

Per quanto riguarda gli aspetti psicologici, le reazioni comportamentali al dolore possono manifestarsi in concomitanza con stati emozionali, come ansia e umore deflesso. La prevalenza dei disturbi dell'umore nella popolazione con dolore cronico è 18-52 per cento e quella della depressione è più elevata che nella popolazione generale. Maggiore gravità dei sintomi depressivi sembra essere associata a più alti

livelli d'intensità algica, sovente caratterizzanti il quadro di una sensibilizzazione centrale (central sensitization).

Anche l'ansia e la preoccupazione cronica sono positivamente correlate con la gravità del dolore, con l'abbassamento della soglia dolorifica e con ridotta tolleranza al dolo- re. L'ansia può impattare sul dolore anche in acuto: è stato, infatti, osservato che il dolore postoperatorio è incrementato da condizioni di ansia, mentre è lenito da un atteggiamento ottimista in fase preoperatoria. La prevalenza di disturbi d'ansia è maggiore nella popolazione con dolore cronico (35 per cento) che in quella generale (18 per cento): per esempio, la manifestazione di disturbo da panico è triplicata nei pazienti con dolore cronico.

[…] L'esperienza viene attivamente processata dalla persona ed è mediata dai significati che le attribuisce. Le credenze negative sul dolore possono impattare sull'adattamento comportamentale al dolore stesso, favorendo l'evitamento e una riduzione delle attività che, a loro volta, contribuiscono alla disabilità e alla percezione di maggiore dolore; inoltre, lo sviluppo e il mantenimento di processi cognitivi negativi e disfunzionali intorno al dolore è favorito dalla comorbilità di una condizione depressiva con quella dolorifica.

Anche le credenze su cause, durata e conseguenze dell'esperienza dolorifica, su quanto sia curabile e su quanto sia compresa dagli operatori sanitari, sono in grado di influenzarla: per esempio, è stato osservato nei pazienti affetti da patologie oncologiche che chi crede che il dolore esperito sia causato dal tumore manifesta livelli di dolore conseguenti ai trattamenti anticancro più elevati di chi crede che l'origine del dolore sia differente. Un'aspettativa negativa, attribuita alla causa del dolore, una scarsa attribuzione di successo alle cure del dolore e la convinzione che il dolore sarà duraturo amplificano intensità e interferenza dolorifica. Al contrario,

uno stato mentale di accettazione, il senso di autoefficacia e la percezione di controllo sul dolore sono in grado di ridurne l'interferenza.

Le credenze e convinzioni sul dolore non solo influenzano la percezione dolorifica, ma anche l'aderenza alle cure e la risposta ai trattamenti: per esempio, possedere un locus of control interno, ovvero credere che i propri stati mentali e le proprie azioni possano avere effetto sull'esperienza dolorifica, riduce l'intensità dei sintomi esperiti e migliora i risultati della presa in carico. È la credenza sulle proprie abilità a essere un significativo determinante di coping efficace e di condizione di benessere.

[…] Infine, è importante ricordare che la relazione della persona con il dolore viene modellata dalle influenze ambientali, a partire dai suoi scambi relazionali precoci, in cui le risposte al dolore possono essere più o meno sollecitate. Le esperienze relazionali apprese di gestione del dolore rimangono dunque in memoria e guidano gli adattamenti successivi al dolore. Relativamente alle influenze delle esperienze pregresse sul dolore, anche gli stili di attacca- mento non sicuri e l'esposizione a eventi traumatici sembrano alterare la percezione algica, determinandone aumento dell'intensità e del rischio di cronicizzazione. Gli stili di attaccamento individuale risultano essere predittivi sia per il successo degli interventi medici e psicosociali sia per gli aspetti relativi alla relazione tra medico e paziente: in altri termini, gli stili di attaccamento possono essere considerati come rilevanti fattori di vulnerabilità psicosociale per la cronicizzazione del dolore acuto.

[…] Dunque, differenti fattori psicosociali, attraverso pattern d'influenza comportamentale, cognitiva e anche neurofisiologica, sono in grado d'influenzare il dolore cronico su più livelli:

- sul processo di generazione di una condizione di dolore cronico, a partire da un danno tissutale, da una patologia o da un dolore acuto;

- sulla condizione di dolore cronico stessa;
- sullo sviluppo di disabilità, a partire dal dolore cronico e sul suo impatto sulla qualità di vita della persona;
- sul livello di disabilità e di carico stesso dell'individuo.

[…] Una valutazione efficace e completa del dolore non può prescindere dall'indagine dei fattori psicosociali coinvolti nell'esperienza algica. Innanzitutto, risulta importante indagare la percezione soggettiva del dolore nell'individuo, sondandone intensità, caratteristiche, tipi di manifestazione e localizzazione. Successivamente, si possono osservare modalità e tempi in cui l'esperienza algica si è generata e si esplica e il suo impatto sulla qualità di vita dell'individuo e sul suo funzionamento. Un assessment completo deve quindi riguardare intensità, durata, localizzazione e caratterizzazione qualitativa del dolore, ma anche eventuali altri sintomi fisici associati, come fatigue, alterazione del sonno o disfunzioni cognitive, sintomi psicologici e caratteristiche di personalità dell'individuo, valutazioni, credenze e significati attribuiti all'esperienza dolorifica e da essa derivanti, come senso di autoefficacia, attribuzione causale esterna o interna del dolore, catastrofizzazione, strategie di resilienza della persona e, infine, contesto sociofamiliare dell'individuo, nonché quelli culturale, valoriale, lavorativo e spirituale.

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1.3 The constructivism

The constructivism can be intended as a post-rationalist orientation of the psychotherapeutic cognitive approach based on the definition of knowledge as

"predominantly tacit construction of ordering". Through this proposal, the conception of an external and real objective world to deal with is abandoned, and it is replaced with the fundamental role attributed to the subjective processing of the information (Mahoney, 1988, 1991). The individual is recognized as a constituent participant of what he observes.

The Italian constructivism (Guidano & Liotti, 1983) sinks its roots in the evolutionary view of knowledge, the Attachment theory (Bowlby, 1982), Piaget's theories on the development of childhood thinking (1970), Lakatos's descriptions of the intrapsychic structure (1974) and Polanyi's (1966) theorizations of the tacit and explicit information processing.

According to the constructivist orientation, the individual must adapt evolutionarily to the environment and, to do so, he actively organizes his cognitive processes: he formulates theories, hypotheses, and expectations which guide from within his action and perception, and which allow him to build his knowledge of the world (Bara, 2007). Therefore, the individual is a complex cognitive system, structurally closed, which organizes itself self-referentially and tends to maintain coherence and continuity of the sense of self through the constant construction of personal meanings (Guidano, 1987, 1991).

The constructivism proposed a radical change respect to the classical cognitivism: the passage from a Universe, i.e., a univocal objective reality which is the same for all, to a Multiverse, in which each world constructed by the observer is equally valid and unique with respect to the others (Maturana, 1978).

Some extracts of a published manual contribution on the psychological interventions for cancer patients are reported to represent, as a paradigmatic example, the way in which I theorized the psychological interventions for patients with neurodegenerative diseases for my PhD Project and how constructivism can be

declined in the psychotherapy. The extracts are in Italian language because the manual contribution was published in Italian language.

1.4 Manual contribution n. 2

Interventi psicologici.

Botto R.

Published on: Torta & Mussa A. Psiconcologia. Il legame tra psiche e soma. Edi-Ermes, 2021

[…] Quando si riceve diagnosi di patologia oncologica si avverte molto spesso un senso di impotenza, di fragilità, di ineluttabilità e di inaiutabilità che si associa alla crisi che si vive, e ci si confronta necessariamente con il tema del limite, relativamente al corpo, alla salute, alle possibilità, alla perdita, al cambiamento, alla prospettiva, al benessere, alla cura, alla morte. Questi sentimenti diventano tipicamente più intensi quando ci si pone nei confronti della patologia con un punto di vista oggettivo su di essa, che porta a constatarne i dati di realtà oggettivi, come le sue caratteristiche biologiche, i suoi effetti sul corpo e sulla salute, il suo stadio, la possibilità di curarla, i rischi ad essa associati, il percorso di cura necessario per affrontarla. L'evento reale di malattia che ci si trova ad affrontare può quindi sembrare schiacciante e la sua contemplazione oggettiva può non dare margine di manovra e di libertà, e può togliere forza e potere. Lo stesso sentire può essere

avvertito dal terapeuta quando prende in carico un paziente oncologico, di cui raccoglie informazioni sulla storia clinica e sulla malattia e il senso di impotenza di fronte ai dati di realtà relativi alla malattia del paziente può sopraffare lo stesso terapeuta.

La chiave per il lavoro è, dunque, il passaggio dal piano oggettivo al piano soggettivo, che porta l'attenzione dalla patologia alla persona che sta vivendo la malattia. Questo cambiamento di prospettiva apre alla possibilità di stare e di fare ed aumenta i gradi di libertà e di movimento nella persona. Il lavoro è dunque sul come si sta con quei dati di realtà, sull'effetto che fanno quei dati di realtà, sugli stati cognitivi ed emotivi ad essi associati, e sul come si può star meglio, su come controllare e modificare questi stati mentali, su come utilizzare le proprie risorse interne ed esterne, su come adattarsi al meglio alla realtà che si sta vivendo. Il punto di vista soggettivo sulla patologia genera quindi spazio di costruzione e di trasformazione e restituisce possibilità ed azione, sia al paziente che al terapeuta.

Una metafora restituisce in modo chiaro cosa si intende con cambio di prospettiva sulla patologia. È come se, quando si riceve diagnosi di cancro, ci si trovasse improvvisamente ai piedi di una montagna ed il mandato fosse di raggiungerne la cima. Subito non si ha idea di come si possa fare, se ce la si farà, come sarà il percorso, e se si riuscirà a raggiungere la vetta. La si riesce a malapena a intravedere e sembra così lontana e così alta. E il disorientamento, la disperazione, l'ansia, lo shock sono intensi. Ma, guardando più vicino intorno a sé, si può scorgere l'inizio del sentiero che porta verso la punta della montagna, e si può decidere di iniziare a percorrerlo, un passo alla volta, da soli o accompagnati, con il proprio zaino di risorse personali. Il percorso potrà essere a tratti duro, impegnativo, si farà molto probabilmente fatica, ci si dovrà fermare per riposare, persone potranno affiancarsi nella salita e poi forse allontanarsi, accompagnare per un tratto o per lungo tempo, il corpo farà male, e non si può sapere fin dove porterà la strada. Ma quello che conta

sarà mettere un passo dopo l'altro, sentirsi, regolarsi, prendersi cura di sé, monitorare le proprie energie, osservare come si sta durante il cammino, provare a mettersi più comodi, liberarsi dai pesi che ostacolano, saper chiedere aiuto quando ne si avverte la necessità, e, anche, vivere il momento ed ammirare paesaggi nuovi che si aprono lungo il cammino.

Questo rappresenta il punto di vista sulla malattia che paziente e terapeuta adottano insieme e che consente il lavoro psicologico. Il terapeuta non affronta il problema oggettivo, ma si occupa del modo soggettivo con cui il paziente sta con il problema oggettivo. Ed il processo di adattamento da favorire non è, dunque, alla malattia, bensì ai cambiamenti che la malattia genera.

[…] La Psicoterapia Cognitivo-Costruttivista si pone nel contesto delle terapie di terza generazione, considerate l'evoluzione della Psicoterapia Cognitivo-Comportamentale.

Il presupposto di tale psicoterapia è che non esista una realtà oggettiva esterna data a priori, bensì un universo di realtà soggettive. L'individuo è inteso come un Sistema Sé, che costantemente attribuisce significati a ciò che vive sulla base di regole interne, al fine di mantenere una propria coerenza interna (Poletti et al., 2017; Guidano, 1987). Il sistema Sé è chiuso ed in continua trasformazione, vale a dire che si riorganizza sulla base delle perturbazioni esterne che riceve al fine di mantenere una propria continuità e identità. Il Sé fa esperienza della vita, ovvero vive l'immediatezza delle esperienze. Allo stesso tempo, se le spiega, ne attribuisce significati, in modo da riuscire ad attribuire a sé l'immediatezza del vivere e mantenere senso di Sé. Il Sé evolve nel tempo integrando gli stimoli esterni come informazioni interne e la costruzione continua di significati è volta al mantenimento di stabilità e coerenza interna. A questo riguardo il Sé può essere più o meno

flessibile, cioè più o meno in grado di assimilare le perturbazioni, e lo scompenso, che tipicamente si manifesta con il sintomo, rappresenta proprio la difficoltà del sistema a far propri nuovi significati a causa di sue rigidità interne (Guidano, 1987).

La psicoterapia cognitivo-costruttivista "lavora non solo sui pensieri, ma su tutti gli stati mentali, come le emozioni e gli stati psicologici incarnati, riferiti al corpo, che sono il nucleo centrale della sofferenza degli esseri umani. Lo strumento del cambiamento è, inoltre, la relazione cooperativa fra terapeuta e paziente, grazie alla quale il paziente prende consapevolezza di come si costruisce il mondo" (Bara, 2009). L'atteggiamento non-giudicante verso i propri stati mentali, osservati anche nel qui ed ora della seduta, favorisce la loro accettazione, che, a sua volta, apre al cambiamento (Bara, 2009).

L'obiettivo della terapia è dunque quello di favorire nel paziente l'acquisizione di consapevolezza su di Sé, sulle proprie caratteristiche e dinamiche interne e sul proprio funzionamento, mediante un lavoro di auto-osservazione dei propri stati mentali e corporei, che va effettuato in assetto di ascolto e lettura curiosi e non giudicanti. Il raggiungimento di nuove consapevolezze, è seguito poi da un lavoro di accettazione dei contenuti di cui si è diventati consapevoli, in quanto parti costitutive del proprio Sé, che vanno accolte come tali e come frutto del divenire del Sé fino a quel momento di vita. Attraverso un atteggiamento mindfulness, il paziente viene addestrato dal terapeuta a de-fondersi dai propri stati mentali, intendendoli come stati passeggeri che così come arrivano se ne vanno, e questo distanziamento aiuta il paziente a non percepirli come pericolosi o destabilizzanti e a non esserne sopraffatto. Questo, a sua volta, ne favorisce l'osservazione non reattiva ed il loro accoglimento gentile come contenuti informativi su di sé. Fa parte di questo processo la riformulazione del sintomo, che consiste nella comprensione e nell'attribuzione di senso ai sintomi fisici o emozionali che si esperiscono, che vanno intesi non come

un qualcosa di disturbante ed estraneo a sé da eliminare, ma come contenuti su di sé informativi, da accogliere, legge ed utilizzare.

Necessariamente la comprensione di sé passa dall'esperienza ed il vivere consapevolmente le esperienze consente la lettura e l'attribuzione di senso agli stati mentali che si attivano durante l'esperienza. Questo è il principio della tecnica della Moviola (Guidano, 1992; Guidano, 2008), molto applicata all'interno di questo tipo di psicoterapia, che consiste nel mettere in Moviola insieme al terapeuta eventi significativi che si vivono, ovvero ricostruirli scomponendoli e ricomponendoli in una sequenza di scene. La scomposizione in scene consente di estrapolare dalla sequenza delle scene e di osservarne gli stati mentali e corporei presenti all'interno (zooming out). Le scene ricostruite, che probabilmente avranno acquisito significati nuovi e diversi, vengono poi reinserite in sequenza (zooming in), la quale sarà a questo punto diversa da come era precedentemente. La scomposizione e ricomposizione della sequenza, unitamente ai movimenti narrativi ed esperienziali del paziente avanti e indietro nella sequenza durante la sua costruzione, possono far luce su certi aspetti vissuti dell'esperienza e portare il paziente ad acquisire nuove consapevolezze legate all'esperienza.

La consapevolezza e l'accettazione costituiscono il presupposto per il cambiamento, ovvero per la trasformazione di quelle dinamiche appartenenti al proprio sistema che consente al sistema di diventare più flessibile, di assimilare più facilmente le perturbazioni esterne, e di evolvere verso una dimensione strutturale più funzionale e adattiva, e di maggiore equilibrio e benessere.

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2. The psychological distress

2.1 Stress and distress

Selye in 1936 defined stress as "the aspecific reaction of the organism to each type of solicitation".

The stressor induces the activation of the hypothalamus-pituitary-adrenal (HPA) axis determining an increased release of cortisol. The axis contributes to the sympathetic activation of the organism in the fight-flight reaction, in which a series of physiological modifications occur to activate the mind-body system to action and coping. Moreover, the endocrine response to stressor is strictly linked to the immune and autonomous ones and to low-grade inflammation (Szabo et al., 2017).

The HPA axis is mediated by the individual's subjective evaluation of the stressor, from which the cascade of psychosomatic responses originates. Thus, the subjective perception of the objective stimulation is fundamental in the stress response and in the adaptation process. In this regard, the subjective experience of an objective disease is of essential importance relatively to the patient's adaptation to the disease and the disease course itself (Torta & Mussa, 2021).

Selye differentiates between eustress, that is the acute and functional stress response, and distress, that is the chronic, pervasive, or too intense dysfunctional stress response (Selye, 1975). Chronic distress is a condition arising from the failing in the adaptation to the stressor during the first phases of response to the stressor: the alarm phase and the resistance phase. Such failing opens to the exhaustion phase in which the stress solicitation remains high or continues, and the individual's stress performance reduces. The exhaustion phase represents the failure of eustress and the creation of the condition of distress (Biondi & Pancheri, 1999).

In case of distress, the elevated stress levels determine a worsening of the individual's biological, emotional, cognitive, and behavioral responses. Distress is characterized by insufficient and not reversible neurotransmitters functions and hyperactivation of the neurotransmitters' receptors; stable and not reversible hyperactivation of the HPA axis; failing in emotional, cognitive, and behavioral coping; and psychological and physical symptoms. In fact, chronic distress is associated to lowering of the immune system, making the individual more prone to inflammation and diseases (Torta & Mussa, 2021).

The National Comprehensive Cancer Network (2013) defined distress as "a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social and/or spiritual nature that may interfere with the ability to cope effectively with a concern. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis".

For these reasons, patients' distress deserves clinical attention to be adequately treated, with the aim to reduce its negative impact on patients' quality life and adaptation to the disease. Finally, since distress is "systemic" because it comprehends multiple aspects and mechanisms, it must be treated in a complex biopsychosocial manner, working on all the elements that characterize it.

Some extracts of a published editorial on emotional aspects in cardiology are reported to represent, as a paradigmatic example, the way in which I theorized the role that the psychological distress plays respect with the medical disease for my PhD Project. The extracts are in Italian language because the manual contribution was published in Italian language.

2.2 Editorial n. 1

Aspetti emozionali in corso di cardiochirurgia.

Botto R., Torta R., Botto R.

Published on: CareAcross, 2021.

Il fatto che le emozioni negative coinvolgessero sfavorevolmente il cuore è stato osservato da Sir William Harvey più di 350 anni or sono, quando egli mise in guardia sul fatto che i disturbi mentali potessero danneggiare il cuore e la circolazione.
Lo stress è stato correlato con le malattie cardiache a partire dagli anni ’50, ma le ipotesi scientifiche del rapporto fra caratteristiche comportamentali e cuore datano dagli anni ’60, quando Rosenman e Friedman ipotizzarono la connessione fra la “personalità di tipo A” e la cardiopatia ischemica, ipotesi solo parzialmente confermata da studi successivi (Rosenman e Friedman, 1962).
Negli ultimi anni sì è sottolineato come i rilevanti interventi chirurgici possano essere associati con un considerevole stress, che, a sua volta, può provocare un pesante impatto negativo sugli esiti degli interventi.

[…] Vari fattori entrano in gioco nella correlazione fra la depressione del tono dell'umore e le complicanze post-chirurgiche: ad esempio la soppressione del sistema immunitario che può esporre i pazienti ad aumentato tasso di infezioni post-operatorie e quindi di incremento di mortalità. Analogamente vanno tenute in conto altre modificazioni biologiche in corso di depressione, ansia cronica e stress cronico quali ad esempio: la attivazione piastrinica, l'incremento della risposta infiammatoria e la manifestazione di disturbi del ritmo (Tully et al., 2012).

Ulteriori problematiche, anche gestionali, possono essere rappresentate dallo sviluppo di disturbi cognitivi, che tendono ad esacerbarsi nel periodo post-chirurgico: tali disturbi cognitivi sono principalmente rappresentati da un deficit della memoria episodica, una ridotta attenzione, una riduzione delle competenze visuo-spaziali, una disfunzione nel processo di informazione e delle competenze esecutive (Neupane et al., 2017).
Inoltre, la depressione sembra rappresentare un fattore indipendente per il rischio di comparsa di un delirio post-operatorio (Nguyen et al.,2018).
Risulta peraltro noto come la presenza pre- e post-operatoria di ansia, depressione e stress cronico possano associarsi con la comparsa di una fibrillazione atriale: in 226 pazienti con chirurgia cardiaca, il 24.8% di essi ha manifestato una fibrillazione atriale incidente, favorita da aspetti somatici (quali un arousal autonomico e situazioni di ansia (Tully et al., 2011).
Una ridotta qualità di vita si osserva in caso di presenza di depressione e ansia dopo chirurgia cardiaca, disturbi che possono persistere anche un anno dopo la chirurgia e possono inoltre favorire la comparsa di nuovi eventi coronarici e quindi riospedalizzazioni. Tali fenomeni sono stati riportati sia dopo CABG (Pinna Pintor et al, 1992; Doering et al., 2007), sia dopo impianti di devices ventricolari (Gordon et al., 2013).

[…] La malattia cardiaca frequentemente induce vissuti di ansia e tristezza, preoccupazioni sulla sopravvivenza, sulle limitazioni e possibile perdita identitaria e di ruoli, con un impatto sulla vita relazionale, ancor più quando il paziente abbia ricevuto un intervento di cardiochirurgia.
Di estrema utilità, in alternativa o in sinergia con gli interventi psicofarmacologici, possono essere utilizzati alcuni interventi psicologici e psicoterapici, individuali o di gruppo.

L’approccio psicoeducativo e gli interventi supportivi, di accoglienza e di counselling aiutano il paziente a comprendere le problematicità psicologiche presenti, a gestire il disagio emozionale e ad utilizzare le proprie risorse interne ed esterne per far fronte alle criticità.

Fra le psicoterapie trova frequente indicazione la terapia cognitivo comportamentale (CBT), mirata a modificare pensieri e/o comportamenti disadattivi (Beresnevaitė et al., 2016; Doering et al., 2016). Le terapie di gruppo sono incentrate sul sostegno reciproco fra i partecipanti e sulla condivisione di strategie ed esperienze per affrontare aspetti problematici della malattia (Benjenk et al., 2018).

In conclusione, anche nel contesto della cardiochirurgia, diviene indispensabile l’attenzione alla presenza nel Paziente di componenti emozionali e cognitive che non solo alterano il senso di well-being del soggetto, compromettendo l’esito degli interventi cardiologici, ma possono influire significativamente sullo stesso decorso e prognosi della malattia somatica. La presa in carico degli aspetti emozionali è quindi necessaria, utilizzando interventi farmacologici mirati (in un giusto bilanciamento fra efficacia e sicurezza) e/o interventi psicoterapici (individuali o di gruppo), in alternativa o in sinergia con i farmaci.

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2.3 The psychological distress in neurodegenerative diseases

Distress is characterized by low grade inflammation, weakened immune system, induced neurotoxicity, reduced neurogenesis, and increased apoptosis. The main consequences of chronic distress are hippocampal and prefrontal atrophy, amygdaloid hyperactivation and dopaminergic dysfunctions. Therefore, significant morphological and functional alterations, caused by chronic stress, can be revealed in the immune, cardiovascular, neuroendocrine, and central nervous systems (Lee & Choi, 2015).

Due to the amount of its noxious effects on the organism, many studies evidenced that chronic stress can negatively influence the pathophysiological modifications of different neurodegenerative diseases, characterized by neuronal loss in different brain structures.

In Alzheimer's Disease (AD), cortisol hypersecretion, due to an over-activation of the HPA axis (Vyas et al., 2016), can accelerate the hippocampal damage processes. In their turn, the hippocampal lesions determine an overproduction of glucocorticoids, and the consequent activation of hippocampal glucocorticoid receptors leads to a reduction in cell survival and neurogenesis and a potentiation of the dendritic atrophy. Furthermore, the corticotrophin-releasing factor is implicated in stress-related enhancing of β amyloid and prolonged stress increases tau

hyperphosphorylation and neurodegeneration (Vyas et al., 2016). AD is also characterized by chronic inflammation that determines an enhancement of proinflammatory cytokines and glucocorticoids release, and an over-stimulation of HPA axis and amyloid precursor protein (APP) expression (Vyas et al., 2016; Machado et al., 2014). Evidence in literature highlight how distress can be effectively considered as a risk factor for AD, due to its capacity of accelerating AD pathogenesis (Machado et al., 2014; Caruso et al., 2018).

Regarding Multiple Sclerosis (MS), HPA axis is activated in most of the cases and seems to favor increasing in disease severity and neurodegenerative levels. In acute phase, great cortisol quantities are associated with a slower disease progression and a minor number of active lesions, due to microglia's eliciting of pro- and anti-inflammatory responses related to neuroprotection. At the same time, the chronic HPA hyperactivity in MS patients is connected to release of neurotoxic factors, exacerbated inflammation and increased neurodegeneration (Melief et al., 2013).

Chronic inflammation is a core feature of Parkinson's disease (PD) in whose etiopathogenetic mechanisms the immune system is strictly involved. In PD, glucocorticoids have a role in the increased vulnerability of the dopaminergic neurons. Pro-inflammatory cytokines levels and cortisol are enhanced, the HPA axis is unbalanced and dysfunctions in glucocorticoids' receptors are registered (Herrero et al., 2015).

Such implications of distress in neurodegenerative diseases can be found also in patients with amyotrophic later sclerosis (ALS), in which inflammatory processes seem to be induced by motor neurons injuries, sending stressful stimuli to the organism. Anti-inflammatory mechanisms of the slow progression phases are replaced by an accentuate pro-inflammatory state in the rapid ones, characterized by high activity of the cytotoxic T cells and production of IL-1, IL-6, and TNF-α. The

mediatory function of neuro-inflammation on the disease progression appears relevant (Thonhoff et al., 2018).

On the other hand, it is well known that chronic distress predisposes to neurodegenerative disorders. In fact, it is associated to a higher risk to develop them (Ross et al., 2018). In this regard, individual's repeated exposure to stressors can affect his physiological functioning and psychological stability and makes him vulnerable to brain atrophy, dementia, and neurodegenerative diseases (Bisht et al., 2018). For instance, animal experiments on AD showed that chronic activation of HPA axis stimulates excitotoxicity and neuronal death, eliciting tau protein antigenic modifications.

According to Selye's general adaptation syndrome theory (1959), stress re-establishes a new internal homeostasis after the impact of a stressor on the organism, independently from its nature (chemical, physical, or psychic). Therefore, psychological concerns can generate distress and are effectively considered as stressing factors. The psychological component of stress is linked to the individual's subjective perception of being able to successfully predict and control a certain stressor (Khalsa, 2015). The psychological and emotional distress, activating the biological, hormonal, immune and autonomic cascade of events, shows the same potential neurodegenerative pathogenicity as the physical perturbations. For instance, depressive symptoms are associated with cognitive decline and an increased risk for AD (Ross et al., 2018). The work-related stress, stress-prone personalities and early life experiences with a stressing psychological burden have been shown to be implicated in the etiopathogenesis of the neurodegenerative diseases, since they can modulate the HPA response to stress (Caruso et al., 2018; Khalsa, 2015). On the contrary, the psycho-socio-spiritual well-being seems to reduce the probability to develop mild cognitive impairment and AD (Khalsa, 2015). Thus, psychological distress plays a significant role in neurodegenerative diseases

and could have clinically relevant implications for the treatment of patients with neurodegenerative diseases.

Regarding the interventions aimed at reducing distress, many studies evidenced the efficacy of the cognitive-behavioral therapy (CBT) and the psychopharmacological treatments also respect to neurodegenerative disorders. In fact, for instance, they can prevent the AD upset (Reid et al., 2017; Wu et al., 2018). CBT has the effect of increasing the cognitive filter on stress perception, while psychopharmacological treatments generally contemplate the use of antidepressants for the regulation of HPA axis activity. They inhibit the release of the pro-inflammatory cytokines, by modulating the glucocorticoids receptor system of the HPA axis, and reduce the levels of cortisol, ACTH, and CRH (Leonard, 2014).

With respect to neurodegenerative diseases, further research on the different forms of psychological distress affecting patients with neurodegenerative disorders could be useful, to better understand form a psychological point of view patients' difficulties in the adaptation and psychological symptoms. Moreover, the most investigated treatments are those aimed at rehabilitating lost functions or preserving from/decelerating the neurodegeneration, i.e., the pharmacological or the neuropsychological ones. On the contrary, the role of psychological treatments aimed at reducing distress seems to be understudied respect to the neurodegenerative processes and further evidence are needed.

3. The PhD project

My PhD project aimed to contribute to research on psychological distress in patients with neurodegenerative disorders.

Not all the neurodegenerative diseases could be considered for reasons of vastness of the theme, feasibility, resources, and time. Thus, only the following were included: AD, Mild cognitive impairment (MCI) prevalently due to AD or Fronto-temporal dementia, MS, and ALS.

The criterion of inclusion of these diseases was merely a criterion of feasibility of the research, explained as follows. After the approval of project by the Ethics Committee, the Units of "Città della Salute e della Scienza" Hospital of Turin dealing with neurodegenerative diseases were considered and the following Units were asked for their collaboration to the project: the Aging Brain and Memory Clinic, the Multiple Sclerosis Center, and the Amyotrophic Lateral Sclerosis Regional Expert Center of Neurology 1 Unit. The project was presented to the Directors of the Centers, and with each center some research projects were implemented according to the aims of the project, literature gaps to solve, and possibilities and limits relative to the recruitment of the participants and the resources to dedicate to each research.

Below the implemented research projects and their relative articles are presented. The articles were then organized into three macro-areas:

- Assessment: articles 1, 2 and 3 which assess different form of distress in patients with neurodegenerative diseases;
- Intervention: articles 4 and 5 dealing with two different psychological interventions to reduce distress;
- Patient-caregiver relationship: articles 6 and 7 relative to patients' caregivers.

Due to the need of further research on psychological distress in patients with neurodegenerative diseases, my PhD project firstly aimed to assess some forms of psychological distress in patients with neurodegenerative diseases.

Anxiety and depression can be considered the principal symptoms due to adaptation difficulties to the disease. Relatively to AD, I found in literature that anxiety and depression in AD have been largely studied. Nevertheless, the pathogenetic explanations of the relationship of anxiety and depression with AD are still not so clear. On one hand, a history of anxiety and depressive disorders, as well as their presence at the first stages of AD, represents a risk factor for the development of dementia. On the other hand, it is well known that neuropsychiatric symptoms and AD share some common biological bases. Moreover, to my knowledge, to date no studies proposed summary explanations of the various reasons why anxiety and depression can appear in comorbidity with AD and during its progression. Most of the published studies on this theme had different aims but presented suggestions that answers to this clinical question in comment to their evidence. Moreover, singly consulted, they offer partial explanations to this clinical phenomenon, that, instead, is complex. Furthermore, other reviews on anxiety and depression in AD did not specifically deal with the pathogenetic hypothesis on their comorbidity and suggest the analysis of the basic mechanisms explaining the prevalence of anxiety and depression in AD. Therefore, according to these considerations, it could be useful to deeper analyse and resume literature evidence on this topic, combining different data and providing a bio-psycho-social frame to explain why AD patients can suffer from anxiety and depression. Hence, I performed a systematic review of the literature on anxiety and depression in AD to better understand why and how AD patients can be affected by anxious and depressive symptoms. See Article n. 1.

In the meanwhile, for the same reasons, I started a longitudinal study at the Aging Brain and Memory Clinic with the initial aim to assess diverse forms of

psychological distress in AD patients at the initial disease phase. However, an adequate recruitment was possible only among patients weekly hospitalized at the Clinic for the neurological assessment of a condition of MCI due to dementia or less. Thus, patients with MCI were recruited for the study, with the clinical hypothesis that also the MCI condition could elicit distress. In fact, in this regard, MCI has significant psychosocial implications. Data from literature indicate the presence of neuropsychiatric symptoms in patients with MCI, including apathy (30-40%), agitation and disinhibition (4-35%), psychosis (3-14%), depression and anxiety (40-50%). Moreover, MCI affects patients' instrumental activities of daily life; this can cause feelings of apathy and a decrease in perceived quality of life. Thus, MCI can have a high psychosocial impact on the individual, and difficulties in the adaptation to MCI condition may arise. Regarding adaptation concerns, demoralization is a clinical condition that originates from failing in coping with a stressful situation. To my knowledge, to date, the construct of demoralization has mainly been investigated in patients with cancer or long-term neurological diseases such as Parkinson's. So, demoralization in patients with MCI has not yet been explored. Thus, fifty-four patients were recruited, and a set of rating scales were administered to them to assess demoralization, distress, depression, anxiety, and cognitive functions. Patients were assessed three times: at T0, during their weekly hospitalization; at T1, 6 months after T0; and at T2, 12 months after T0. Twenty-five patients were evaluated at T1, and 17 at T2. The Article n. 2 is the first paper written relatively to this project. It analyses patients' demoralization and distress at T0 and its relationship with the cognitive performance.

During this longitudinal study, I met many carers assisting their loved ones. Literature on carers evidence that great commitment and many resources are required for carers of patients with dementia, leading to a significant burden and increasing the risk of physical and psychological morbidity. Instead, carers of patients with MCI

identify less with the caregiver role because of the reduced impact of MCI on daily functioning. At the same time, anticipatory grief and loss seem to be the main clinical aspect involving them: carers of patients with MCI can feel the loss of pre-existing relationships, control, and hope, and can be worried and uncertain about the future and their capacity to continue in caregiving the patient. Therefore, I decided to insert in the project also a carers' evaluation, with the aim to investigate possible forms of distress affecting carers that could have reverberations with the patients' distress. Thus, at T0, the patients' carers were invited to fill a set of scales investigating demoralization, burden, anxiety, depression, and coping with the aim to firstly assess demoralization and to investigate its association with carers' burden, anxiety, depression, and coping styles. Then, the second aim was to evaluate the association between carers' demoralization and patients' psychological and cognitive symptoms. See Article n. 6.

Another research project was developed with the Multiple Sclerosis Center. About MS, It is known that, for the fact of being a chronic, symptomatic, and unpredictable disease, with no resolutive treatments, MS has a significant impact on the individual, reducing his quality of life and causing psychological distress. Thus, MS diagnostic communication can be a critical and stressful event for patients and the period surrounding MS diagnosis is undoubtedly emotionally intense. Nevertheless, to my knowledge, to date, only a few studies provided evidence on the psychological adaptation to the MS diagnosis during the early stages of the disease. Moreover, they all were cross-sectional and they did not investigate a narrow time range after the diagnosis. Therefore, to provide further evidence on the theme, I developed a study with the first aim to assess distress, post-traumatic stress, anxiety, depression, and demoralization in relapsing-remitting MS (RR-MS) young adults who received the diagnosis at the most for six months. Secondly, the study aimed to explore the association between these forms of psychological distress and coping, quality of life,

fatigue, and cognitive impairment. Finally, it aimed to longitudinally test if psychological distress varied or less during the following year. . Fifty-six patients were recruited, and they were invited to three evaluations: at T0, in the six months after the diagnosis; at T1, six months after T0; and at T2, twelve months after T0. A total of 28 patients received the T1 evaluation and 24 the T2 evaluation. The Article n. 3 is the first written on the project and it presented the evidence emerging from the longitudinal assessment.

Some research ideas were discussed with the Amyotrophic Lateral Sclerosis Regional Expert Center. The colleagues of the Center proposed a research reflection on Westeneng and colleagues' prognostic model for ALS. In fact, due to its characteristics the model is nowadays widely used in both basic and clinical research and it is definitely useful for estimating patients' prognosis. Nevertheless, its application in the clinical practice may be more complicated due to, for example, cultural, spiritual, personal aspects dealing with the prognostic communication and more debate over the theme could be relevant. Therefore, we performed a study with the aim to open this discussion through the investigation among Italian neurologists with experience on ALS of their knowledge of this model, the frequency of their use of the model in neurological practice and their general and spiritual attitude toward prognostic communication. Thus, an ad-hoc survey was created to be administered to a sample of Italian neurologists and the evidence coming from the research were included in the PhD project. See Article n. 7.

Finally, relatively to interventions, two studies were performed.

Firstly, it is known that autogenic training (AT) is a standardized relaxation technique used to balance sympathetic tone and parasympathetic tone. AT has been evidenced as an effective integrative treatment in various medical diseases. More specifically, AT induces muscle and mental relaxation, which can lead to a reduction

in stress and anxiety levels in chronic diseases that can be characterized by a long-term stress reaction, such as asthma, hypertension, tension-type headache, and psychosomatic disorders. Thus, I would like to implement a narrative review aiming to summarize the applications of AT to patients with neurodegenerative diseases and their effects. Unfortunately, very few studies on this relaxation technique are published on samples with neurodegenerative diseases and, more in general, with organic diseases. For this reason, the review considered not only neurodegenerative diseases but also all the other categories of diseases for which clinical trials on autogenic training were performed. See Article n. 4.

The other study on interventions originated from my passion for psychotherapy and from the great and well-known potential that psychotherapeutic interventions also have in the medical field. In this regard, data from randomized trials and neuroimaging confirm the positive effects of psychotherapy in MS patients. Cognitive-constructivist psychotherapy is my psychotherapy approach with patients and it is a particular type of cognitive-behavioral therapy that acts in the direction of reorganizing a patient's immediate and implicit experience into more understandable and manageable explicit maps. It has the aim to favor the patient's awareness of his meanings, reactions, and internal functioning, with the hypothesis that better knowledge means better management and the possibility of changes towards more functional ways of giving meaning to events and responding to them. Research on psychotherapy in general are increasing, but there is a need to increase them, and, to my knowledge, to date, no research has been published yet on the cognitive-constructivist psychotherapy in the neurodegenerative field. Thus, I decided to present a case report on a brief intervention of cognitive-constructivist psychotherapy with a patient with RR-MS.. See Article n. 5.

4. Assessment

4.1 Article n. 1

Anxiety and depression in Alzheimer's disease: a systematic review of pathogenetic mechanisms and relation to cognitive decline.

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ABSTRACT

Objectives To explore the pathogenetic hypothesis provided to explain the comorbidity of anxious and depressive symptomatology and AD and to assess the association between anxious and depressive symptoms and the AD-related cognitive impairment.

Methods In October 2020 and March 2021, PsycINFO, Embase, Ovid and CINAHL were searched for peer-reviewed original articles investigating anxiety and/or depression in AD.

Results 14760 studies were identified and 34 papers on AD patients were included in the review.

Suggested biological causes of depression and anxiety in AD include higher Strychnine-sensitive glycine receptors (GlyRS) functioning and selective reduction of N-methyl-d-aspartate (NMDA) receptor NR2A density, cortical and limbic atrophy, lower resting cortical metabolism, lower CSF Aβ42 and higher t-tau and p-tau levels, and neuritic plaques. At the same time dysthymia arise in the early stages of AD as an emotional reaction to the progressive cognitive decline and can cause it; anxiety can appear as an initial compensating behaviour; and depression might be related to AD awareness and loss of functional abilities. Affective symptoms and the expression of the depressive symptoms tend to reduce as AD progresses.

Conclusion The neurodegeneration of areas and circuits dealing with emotions can elicit anxiety and depression in AD. In the early stages of the disease, anxiety and depression could arise as a psychological reaction to AD and due to coping difficulties. In late AD stages, the cognitive impairment reduces the emotional responses and their expression. Anxiety and depression are more intense in early-onset AD, due to the major impact of AD on the individual.

KEYWORDS

Anxiety, depression, Alzheimer’s disease, psychological symptoms, dementia.

INTRODUCTION

Alzheimer’s disease (AD) is a primary neurodegenerative dementia and one of the leading causes of disability in older people [1]. AD is clinically characterized by a progressive, global cognitive impairment that affects a person's ability to perform everyday activities and is associated with brain changes that involve the extracellular accumulation of beta-amyloid plaques outside neurons and intraneuronal deposition of tau tangles inside neurons [2].

Although the core symptoms of AD are memory impairment and deficits in other cognitive domains [3], neuropsychiatric symptoms such as anxiety and depression are commonly observed during the clinical course of the illness [4, 5]. In AD, the prevalence of anxiety ranges from 9.4% (preclinical phase) to 39% (from mild to severe decline) [6, 7] and the prevalence of depression in mild to moderate AD varies from 14.8% [8] to 40% [9]. Anxiety is generally characterized by excessive worry, tenseness, irritability, wandering and decreased engagement in once pleasurable activities [10]. Anxious symptoms seem to be associated with more severe impairments in activities of daily living and worse behavioural concerns [11], and anxiety could be considered as a psychological response to AD diagnosis [12]. Typical depressive symptoms in AD are insomnia, social withdrawal, reduced purpose-oriented behaviour, loss of interest in once-enjoyable activities and hobbies, guilt, hopelessness, and sadness [13]. Anxiety and depression often overlap, especially in patients with mild AD [14].

Nevertheless, despite this evidence, due to progressive cognitive deterioration and to diagnostic and methodological difficulties in assessing anxiety and depression in AD patients, it is not easy to evaluate their role with respect to the progression of the disease.

Anxiety and depression in AD have been largely studied. Nevertheless, the pathogenetic explanations of the relationship of anxiety and depression with AD are still not so clear. On one hand, a history of anxiety and depressive disorders, as well as their presence at the first stages of AD, represents a risk factor for the development of dementia [15, 16]. On the other hand, it is well known that neuropsychiatric symptoms and AD share some common biological bases. Moreover, to our knowledge, to date no studies proposed summary explanations of the various reasons why anxiety and depression can appear in comorbidity with AD and during its progression.

It is known that anxiety and depression can manifest during AD, and there are always causes explaining psychological symptoms. Thus, why AD patients can suffer from anxiety and depression? Which are the causes for the occurrence of these symptoms in patients with AD?

Research on the theme is heterogeneous relatively to the aims and the methodology of the studies. Most of the published studies on this theme had different aims but presented suggestions that answers to this clinical question in comment to their evidence. Moreover, singly consulted, they offer partial explanations to this clinical phenomenon, that, instead, is complex. Furthermore, other reviews on anxiety and depression in AD did not specifically deal with the pathogenetic hypothesis on their comorbidity and suggest the analysis of the basic mechanisms explaining the prevalence of anxiety and depression in AD [6, 17, 18].

Therefore, according to these considerations, it could be useful to deeper analyse and resume literature evidence on this topic, combining different data and providing a bio-psycho-social frame to explain why AD patients can suffer from anxiety and

depression. Hence, this systematic review had the aim to collect the evidence published to date that let answer to the above-presented clinical question. This question can be declined into two sub-hypotheses: anxiety and depression in AD could be due to pathogenetic mechanisms and there could be a relationship between them and cognitive decline. Thus, the purpose of this systematic review was to explore the pathogenetic hypothesis provided to explain the comorbidity of anxious and depressive symptomatology and AD and to assess the association between anxious and depressive symptoms and the AD-related cognitive impairment.

METHODS

The systematic review (PROSPERO registration n. CRD42019126592) was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [19]. The study was approved by "Comitato Etico Interaziendale A.O.U. San Giovanni Battista di Torino A.O. C.T.O./Maria Adelaide di Torino": protocol number 0034410, procedure number CS2/1179, date of approval: 29/03/19.

Search strategy

The literature search was performed in October 2020 on PsycINFO, Embase, Medline and CINAHL databases. Then, a search update followed in March 2021 on the same databases. The search was conducted by L.C., a librarian expert in data extraction from databases, using keywords including the following terms (MeSH and free words): ("Alzheimer's disease" [MeSH] OR (Alzheimer disease) OR (Alzheimer) OR Dementia [MeSH]) AND ("Anxiety" [MeSH] OR (Anxiety Disorder) OR (anx) OR "Depression" [MeSH] OR (Depressive Disorders) OR (Stress, Psychological)). See online resource "SM 1" for the details of the search strategy.

Study eligibility criteria

Only full-text original articles published in English language on peer-reviewed journals were included in the search. In detail, studies with longitudinal, prospective, cross sectional, multicentre, evaluative, or comparative designs, and not assessing interventions were analysed. Furthermore, studies had to be on patients with a diagnosis of AD. Diagnosis of AD had to be done using approved diagnostic criteria i.e., those of DSM-III-R, DSM-IV, DSM-IV-TR, NIA-AA, NINCDS-ADRDA, ICD-10, CERAD, and Braak stage. No age-filters were used. Finally, they had to investigate symptoms of anxiety and/or depression; then, they had to propose pathogenetic hypothesis on anxiety and depression in AD and/or to investigate the association between anxiety and/or depression and cognitive impairment.

The exclusion criteria were: 1. Literature reviews; 2. Systematic reviews; 3. Meta-analysis; 4. Case-reports or case series studies; 5. Clinical trials; 6. Studies not including patients with AD (i.e., studies including patients with Frontotemporal Dementia, Vascular Dementia, Parkinson Disease, Mixed Dementia, post-traumatic dementia, Huntington Disease, Dementia with Lewy Bodies, and HIV-associated dementia); 7. Studies not evaluating anxiety or depression; 8. Studies evaluating anxiety or depression but not proposing pathogenetic hypothesis on anxiety and depression in AD or not investigating the association between anxiety and/or depression and cognitive impairment; 9. Studies not published and not peer-reviewed; 10. Health policies and guidelines.

Studies of grey literature (theses, abstracts, books, dissertations) were not included in the search considering the high number of peer-reviewed articles published on the topic.

No limitations were established on publication data of the studies. No limitations were established on methods of anxiety and depression assessment on condition of

this criteria: studies had to assess anxiety and/or depression using validated scales or structured interviews.

Data collection and analysis

Two researchers (NC and AC) identified the potential studies of interest, screening titles and abstracts. All the studies that did not meet all the inclusion criteria or that complied with almost one exclusion criteria were excluded.

Then, the remaining studies were screened reading their full text, and the selected articles were revised to verify whether they fulfilled the inclusion criteria. If there was any disagreement in the study selection, a third investigator (RB) read the article and NC, AC and RB decided together for the inclusion of the article in the review or not.

All the studies selected for the review were revised considering country, objectives, design, sampling and sample size, outcome measures, and results.

Any direct contact with authors was necessary with the following exception: for Panegyres et al.'s study [20] information was missing for the tools used to assess anxiety and depression. So, the responsible for the C-Path Online Data Repository used by authors was contacted and they provided the missing information.

Risk of bias

We assessed the quality of the included articles using the Newcastle–Ottawa Quality Assessment Scale (NOS) [21], a standardized instrument used to critically review nonrandomized studies with its design and content. Two independent investigators (A.C. and N.C.) analysed each article. Scores ranged from 0 to 9 points, with higher scores indicating higher study quality. We considered NOS scores of 0–3, 4–6, and ≥ 7 to indicate low, medium, and high quality, respectively.

RESULTS

The identified potentially relevant studies, resulting from the searches on the above-mentioned databases, were 14760. Of these, 4700 were on PsycINFO, 1351 on Embase, 4738 on Ovid and 3971 on CINAHL. After comparison of the databases, 3888 duplicates were removed.

Screening titles and abstracts, 10798 studies were identified as not meeting the inclusion criteria or fulfilling almost one exclusion criterion and were excluded.

Then, the full texts of the 74 articles considered relevant for the inclusion in the review were analysed. Of those, 40 were excluded because they did not meet the inclusion criteria, or they meet almost one exclusion criterion.

Finally, 34 papers were included in the systematic review after the end of the screening process.

The selection procedure is represented through a flow diagram in the online resource "SM 2".

Methodological aspects

Country. 15 studies were conducted in the USA [22-36], 2 in Germany [37, 38], 2 in the Netherlands [39, 40] (Banning et al. [35] conducted their study both in USA and in Netherlands), 1 in Singapore [41], 2 in Japan [42, 43], 1 in Sweden [44], 2 in Argentina [45, 46], 3 in England [47-49], 1 in Australia [20], 2 in France [50, 51], 1 in Italy [52], 1 in China [53] and 1 in Norway [54].

Objectives. Of the 34 studies, 17 explored the pathogenetic hypothesis that explain the comorbidity of AD, anxiety and/or depression. Among these, 4 evaluated the association between anxiety, depression, and AD biomarkers; 8 evaluated whether anxious and depressive symptomatology in AD arise after the diagnosis of AD or as

a reaction to perceived cognitive decline. 10 studies investigated whether anxiety and/or depression can influence the cognitive functions, 3 evaluated the prevalence of depressive and anxiety symptoms, 2 assessed the trajectories of depression, 1 examined if depression is a risk factor for the onset of AD and 1 study explored clinical differences between early onset AD and late onset AD patients.

Study design. Of the 34 studies, 12 were longitudinal, 9 were cross-sectional, 1 was a comparative study, 1 was a multicentric study, 5 were prospective studies, 2 were retrospective studies, 1 was a cohort observational study, 2 were prospective longitudinal studies and 1 was retrospective longitudinal study.

Sample. The samples consisted of 12512 elderly patients with diagnosis of AD or with probable AD in total. All the screened studies included both genders, predominantly women (56,4%). Patients' mean age was 73.82 ± 6.8 yrs (range = 57.7 - 86.2). Relevant variability among studies was observed in the number of participants. Sample sizes ranged from 20 to 3747 AD patients.

The AD duration varies between studies: in 14 studies, patients suffered from AD from less than six years and in 5 studies patients suffered from AD from at least seven years. The authors of the remaining studies did not provide precise data on AD duration.

At the time of the assessment, most patients were in a mild to moderate AD stage. Only in 4 studies, participants were patients with severe AD [24, 39, 41, 47].

In addition to AD, patients also showed a comorbidity of depression and/or anxiety. Of all the samples, 18 consisted of subjects with AD and depression, 5 consisted of subjects with AD and anxiety and 5 included subjects with a comorbidity of AD, depressive and anxious symptoms. In the other samples, during the study, patients with AD developed depression or anxiety.

About the samples of the included studies, only 2 of them were from psychiatric settings [28, 38] and only 1 was from primary care [26]. Most samples were from dementia specialty clinics. Among them, 15 were from outpatient settings, 4 were inpatient settings, 2 nursing home settings and 3 in-home settings. The other remaining studies, instead, did not provide further information on the sample.

Outcomes assessment. For AD diagnosis, 26 studies used criteria established by the NINCDS-ADRDA [55] and 1 study [36] also used NIA-AA criteria [56]. Two studies [38, 54], instead, used ICD-10 diagnostic criteria; while the Diagnostic and Statistical Manual of Mental Disorders third edition revised (DSM III-R) [57] and the fourth edition (DSM IV) [58], have been used in 6 studies, respectively, for AD diagnosis [29, 43, 44] and for dementia diagnosis [35, 36, 40]. In one study [39], AD diagnosis was neuropathologically confirmed in post-mortem using the Consortium to Establish a Registry for AD (CERAD) criteria [59].

Few studies [39, 41, 48] also performed the staging of the severity of AD neuropathology, using the Braak staging scheme [60]. For the assessment of the cognitive impairment, the Mini Mental State Examination (MMSE) [61] was used in almost all the studies.

Most studies evaluated anxiety and depression using the Neuropsychiatric Inventory (NPI) [62], the DSM III-R/DSM IV criteria [57, 58], the Hamilton Depression Rating Scale (HDRS) [63] and the Hamilton Anxiety Rating Scale (HARS) [64].

Risk of Bias Assessment

The risk of bias assessment of the included studies showed high quality design in most of our studies (25 out of 34), while the rest appeared with a medium risk of bias (9 out of 34). A closer analysis revealed that most of the research did not clarify the duration of the follow-up or how many patients concluded it; some articles lost "stars" within the "comparability category; finally, several studies did not specify in

detail the history of the investigated disease. Table in the online resource “SM 3” shows the results of the risk of bias assessment, specifying with how many “stars” we evaluated each included study.

Results.

Pathogenetic hypothesis for anxiety, depression, and AD comorbidity.

Depression and anxiety occurring throughout the AD course both due to brain damage and psychosocial factors [43, 49, 54].

Higher anxiety levels seemed to be associated with higher Strychnine-sensitive glycine receptors (GlyRS) functioning and selective reduction of N-methyl-d-aspartate (NMDA) receptor NR2A density [41]. Anxiety in AD could be explained by the atrophy in the right precuneus and inferior parietal lobule and hyperperfusion of the bilateral anterior cingulate cortex [42]. Higher anxiety was associated with lower resting metabolism in the bilateral entorhinal cortex, anterior parahippocampal gyrus, left anterior superior temporal gyrus and insula [30].

Depression was associated with AD patology, i.e., lower CSF Aβ42 and higher t-tau and p-tau levels [36], to atrophy of the insula, the inferior frontal lobe, and the limbic neural networks, and to changes in the temporal and parietal regions, including supramarginal, superior and inferior temporal and fusiform gyri, right posterior cingulate and precuneus, locus coeruleus and basal nucleus of Meynert [22, 35, 44, 47, 53]. Depression can be determined by decreased cortical metabolism, neuritic plaques, and neuronal damage in the temporal cortex that lead to disinhibition of the HPA-axis. On the other hand, the association between depression, HPA hyperactivity and cardiovascular disease can determine AD progression [39]. AD developing seems to stop the continuity of the depressive state due to impaired memory and executive control [32]. Affective symptoms and the expression of the

depressive symptoms tend to reduce as AD progresses [48, 53]. Dysthymia was primarily in the early stages of AD, as an emotional reaction to the progressive cognitive decline, while major depression may be related to biological factors and is symptom of the neurodegenerative AD processes [26, 38, 45].

Banning et al. [35], explained anxiety in AD as an initial compensating behaviour. While depression could be more related to AD awareness or to the psychological reaction to AD, and to relational and biological factors [36]. Depression can also be reactive to AD-related loss of functional ability [29, 31, 33].
Anxiety and depression were higher in patients with early-onset AD compared to patients with late-onset AD due to the following factors present in early-onset AD patients: greater changes in lifestyles, roles, and responsibility; poor social adjustment; cognitive impairment; dementia severity; and more rapid progression [34, 43, 49, 20]. Van Vliet [40] evidenced that in late-onset AD depression was more persistent and was the most prevalent symptom, probably due to contextual factors, i.e., death of a loved one or physical disability.

Association between anxiety, depression, and cognitive impairment.
Cognitive impairment seemed to mediate the association between the presence of anxiety, lower CSF levels of Ab42 and higher levels of CSF t-tau and p-tau [35]. Lower inhibition performance on Stroop test was associated with subsequent higher risk of anxiety and depression, due to the involving of anterior cingulate cortex [51]. Association of depressive symptoms and cognitive impairment seems to be independent of cortical plaques and tangles [25].

Depressive symptoms in AD were associated with a greater severity of cognitive impairment [26, 28, 37] and additional cognitive impairment, i.e., frontal planning impairments, disappear or improve with remission of depression [52].

Depression did not increase as mild cognitive impairment developed [32]. It could be an early reaction to perceived cognitive decline [50].

Depression can cause cognitive impairment [48, 54], but it seems to have no impact on cognitive functions during the early and advanced stages of AD [48].

Cognitive impairment was associated with a small reduction in mood symptoms and a modest increase in somatic symptoms: the AD progression determines the degradation of the ability to experience or express emotion [27].

A summary of the 34 studies included in the systematic review is reported in Table 1.

DISCUSSION

The review aims to provide a bio-psycho-social frame to explain why AD patients can suffer from anxiety and depression, considering the phenomenon in its complexity. Thus, multiple punctual evidence has been combined to resume and conceptualize the literature state of the art on reasons underlying the comorbidity between anxiety, depression, and AD. For this reason, the results of the studies analysed in this review are heterogeneous because they consider biological, but also psychosocial aspects and they deal with AD in all its different phases relative to its progression. They evidence that both anxiety and depression could be due to brain damage on one hand and psychosocial factors on the other.

The neurodegeneration of neural areas and circuits dealing with emotions can determine hyperactivation and disinhibition of the HPA axis, that can elicit the anxious and depressive symptoms. In this regard, it has been hypothesized that hyper perfusion and atrophy of cerebral areas - i.e., anterior cingulate cortex, praecuneus and parietal lobule-, but also receptor alterations - i.e., NMDA receptor- could be

linked to depressive symptoms [41, 42]. This condition of chronic distress, in turn, can lead to neurodegeneration and contribute to AD progression. Then, during the late AD stages, the high rate of brain damage could stop the depressive condition due to the impairment of memory and the executive functions, and the intensity and expression of the affective symptoms are reduced. This phenomenon could be present because a more severe cognitive decline is frequently associated with loss of insight in AD [65]. Stronger negative emotions require a good cerebral function: if the cognitive impairment is too serious, patients will not be able to produce this type of emotional response [27, 37].

On the other hand, the early stages of AD seem to be characterized by dysthymia, as an emotional reaction to the cognitive decline, and anxiety, as an initial compensating behaviour. During the initial phases of AD, depressive symptoms can manifest due to AD awareness, the impairment of the socio-relational functioning and the loss of functional abilities. Thus, in this phase, anxiety and depression could arise due to difficulties in the adaptation to the disease and represent the psychological response to the loss of self-sufficiency and independence [14, 15, 35]. Instead, major depression could be more related to biological factors, such as neurotransmitters and endocrine alterations or cortical apoptosis.

Literature evidence also differences in anxiety and depression between early-onset and late-onset AD. They seem to be more intense in early-onset AD due to more changes in lifestyles and life roles, to more responsibilities to cope with and to a poorer social adjustment to the disease. Moreover, early-onset AD is often characterized by more rapid progression, dementia severity and cognitive impairment and this can promote the psychological symptoms. The late-onset AD can occur in the elders in comorbidity with other concerns, such as physical disability or bereavements. Thus, in late-onset AD depressive symptoms are the most prevalent and seem to be more persistent.

The results of the studies show an association between anxiety, depression, and cognitive decline. Anxious and depressive symptoms can manifest as an initial psychological reaction to the cognitive impairment. Furthermore, on its turn, depression can impact on the cognitive functioning, causing an increase of the cognitive deficits: i.e., during the remission of the depressive symptoms, the capacities of planning mediated by the frontal circuits improve. This role of influence of depression on cognition has been observed only in the intermediate AD phases.

Finally, higher cognitive impairment is associated with higher somatic symptoms of anxiety and depression and lower affective symptoms. This could be due to reduced metacognitive possibilities to experience and express emotions.

The methodology of the symptoms' assessment could have moderated the abovementioned findings.

Assessment tools more specifically dedicated to the analysis of anxiety and depression in AD can estimate symptoms differently than those provided by more generic criteria, such as the DSM or the ICD [66, 67]. In this regard, Vilalta-Franch and colleagues [67] hypothesized that the degree of rigidity of the included criteria could influence the diagnosis. Furthermore, they observed that the use of the Neuropsychiatric Inventory (NPI) can be biased by the fact that caregivers usually overestimate patients' depressive symptoms due to their own distress [68, 69].

The minority of studies performed longitudinal research designs, so further research with longitudinal observations is needed to better explore the variation of anxiety and depression along the AD course. Moreover, few studies assessed the AD severity, despite it emerged as a factor playing a role with respect to the considered psychological symptomatology. Another limitation of the studies is that they have used different AD diagnostic criteria, such as NINCDS-ADRDA, NIA-AA, DSM, and ICD. Furthermore, NINCDS-ADRDA, although is the most used and more valid than the others diagnostic criteria, is less accurate than the currently used NIA-AA criteria. Large criteria for source search have been preferred to more stringent ones

to collect and mix more evidence. At the same time, they reduced quality and homogeneity of evidence. In fact, NOS scores indicated that the quality of the included studies is not high, and studies were heterogeneous in aims, types of assessment, sampling, participants, AD duration, and neuropsychological assessment, that in most cases was not adequate. In this regard, also time impacted on methods heterogeneity between older studies and the more recent ones, because the assessment criteria have changed and improved over time. Implementing more circumscribed reviews could preserve research quality and favour a more specific, detailed, and reliable comprehension of the described clinical phenomena. Moreover, most studies assessed anxiety and depression when AD was mild or moderate and not severe: this is understandable considering the serious cognitive decline that characterizes the AD advanced phases and hinders the psychological assessment, but, at the same time, it limits the exploration of anxiety and depression in patients with severe AD. Finally, AD is often present in comorbidity with dementias due to other causes, such as the vascular one. So, it would be useful to study anxiety and depression also in clinical condition of multiple dementias.

Conclusion

The neurodegeneration of areas and circuits dealing with emotions can elicit the anxious and depressive symptoms that, in their turn, can lead to neurodegeneration. In the early AD stages, anxiety and depression could arise as a psychological reaction to the disease and due to difficulties in the adaptation to AD. During the late AD stages, the serious cognitive impairment reduces the emotional responses and their expression. Finally, anxiety and depression are more intense in early-onset AD, due to the major impact of AD on the individual.

Further research, especially with longitudinal design, considering all the AD stages, performing adequate neuropsychological assessment, and investigating psycho-

social factors are needed to better clarify the comorbidity between depression, anxiety, and AD.

STATEMENTS AND DECLARATIONS

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Comment

In the discussion section, it could be useful to include a specific sub-paragraph about limitations and future directions in which indicating other interesting research aspects, such as implementing studies to define the most complete and adequate AD neuropsychological assessment that can identify neurological and psychological symptoms, and to study relevant psychosocial factors, such as the disease awareness, the existential distress, or the attachment style, that could deal with depression and anxiety in AD.

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TABLES

Table 1. Characteristics of the included studies.

Study		
Banning et al. [36] USA	**Objective**	To assess depression over a 5-years follow-up period and to relate its trajectories to AD biomarkers
	Study design	Retrospective longitudinal study
	Sample	3030 Pt with AD; Gender: n.a.; Age: nd.; Dementia severity: prodromal
	Outcomes	AD criteria: DSM-IV-TR, NIA-AA and NINCDS-ADRDA
	Assessment	Cognitive abilities assessment: MMSE Depression Assessment: NPI and NPI-Q
	Results	Association between increasing probability of depression over time and AD pathology, i.e., lower CSF Aβ42 and higher t-tau and p-tau levels.

		Association between AD pathology and de novo or (initially) rising symptoms of depression.
Banning et al. [35] USA	**Objectives** **Study design** **Sample** **Outcomes assessment** **Results**	To study (inter)relations of AD biomarkers and neuropsychiatric symptoms in AD dementia and the impact of the cognitive functioning. Retrospective cross-sectional study 626 Pt with AD; M:299; F:327; Age: 73.9; Dementia severity: mild level AD criteria: NINCDS-ADRDA and DSM-IV Cognitive abilities assessment: MMSE Anxiety and Depression Assessment: NPI, NPI-Q Association between the presence of anxiety and lower CSF levels of Ab42 and higher levels of CSF t-tau and p-tau, mediated by MMSE. No association between depression and Ab42 values, t-tau, p-tau, and reduced hippocampal volume (HCV) and between anxiety and HCV. Association of anxiety with AD pathology, due to impaired cognitive functioning, as initial compensating behaviour. Depression more related to psychosocial (i.e., awareness and psychological reaction to AD) or environmental (i.e., relationship

		with caregivers) or other biological factors (i.e., HPA axis or chronic inflammation).
Rouch et al. [51] France	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To evaluate the association between cognitive functioning and the occurrence of Behavioral and Psychological Symptoms of Dementia Prospective study. Pt were assessed at 6,12 and 18 month follow-up 237 Pt with prodromal or mild AD; M:100; F:137; Age:79,5; Age at onset: n.a.; Dementia severity: mild level AD criteria: NINCDS-ADRDA Cognitive abilities assessment: MMSE, Anxiety and Depression Assessment: NPI Association between lower inhibition performance on Stroop test and subsequent higher risk of anxiety and depression. Stroop test involves anterior cingulate cortex, that is involved in depression
Wu et al. [53] China	**Objective** **Study design**	To explore the probable neuroanatomical substrate of depressive symptoms of AD patients. Cross-sectional study with control group

	Sample **Outcomes** **Assessment** **Results**	20 Pt with AD; M:11; F:9; Age: 67.15; Dementia severity: CDR 0.5-2 normal to moderate AD criteria: NINCDS-ADRDA Cognitive abilities assessment: MMSE, ADL Anxiety and Depression Assessment: HAMA and HDRS Negative association between depression and insular and inferior frontal lobe grey matter volume, controlling for MMSE. Atrophy of the insula and the inferior frontal lobe more severe for depressed patients. Due to insular degeneration, depressive symptoms in AD could be related to abnormal somatic sensations; affective symptoms tend to reduce as AD progresses.
Baillon et al. [49] England	**Objective** **Study design** **Sample**	To compare neuropsychiatric symptoms (NPS) in people with early-onset Alzheimer's disease (EOAD) and late-onset AD (LOAD). Retrospective 24 Pt with EOAD (< 65 years), M: 11; F:13; 56 patients with LOAD (> 65 years), M: 20; F: 36. Mean age: 59.3 EOAD, 82.3 LOAD. Duration of

		illness (months): 50.3 (41.8) EOAD, 26.9 (22.7) LOAD. Dementia severity: mild level
	Outcomes	AD criteria: NINCDS-ADRDA
	Assessment	Cognitive abilities assessment: MMSE, Bristol Activities of Daily Living Scale (BADLS) Anxiety and Depression assessment: NPI.
	Results	Anxiety and depression higher in patients with EOAD compared to patients with LOAD. Diagnosis and AD-related changes in lifestyles, roles and responsibility are greater in EOAD patients. Depression and anxiety occurring throughout the AD course both due to brain damage and psychosocial factors.
Barca et al. [54] Norway	**Objective**	To investigate the different trajectories of depressive symptoms among patients with AD and the relationship between the progression of AD and different trajectories.
	Study design	Longitudinal observational study.
	Sample	282 Pt (177 with dementia due to AD and 105 with prodromal AD); M:130; F:152; Age: 73.2; AD Duration: n.a.; Dementia severity: mild level
	Outcomes	AD criteria: ICD-10; NINCDS-ADRDA

	Assessment	Cognitive abilities assessment: MMSE Depression assessment: Cornell Scale for Depression in Dementia and Clinical Dementia Rating Scale (CDR)
	Results	Identified three distinct trajectories of depressive symptoms: stable low-average; high and decreasing; moderate and increasing. Association between the trajectories and AD progression: more depression in faster dementia. faster progression leads to organic depression due to brain damages. Depression could also occur as a psychological reaction to greater impairments and can cause cognitive impairment.
Tanaka et al. [43] Japan	**Objective**	To investigate the relationship between dementia severity and behavioural and psychological symptoms in early-onset AD patients.
	Study design	Cross-sectional.
	Sample	92 Pt with early-onset AD; M:31; F:61; Age: 59.0; AD Duration (years): 5.6; Dementia severity: mild to severe
	Outcomes	AD criteria: NINCDS-ADRDA
	Assessment	Cognitive abilities assessment: MMSE

	Results	Depression and anxiety assessment: Neuropsychiatric Inventory No differences in depression and anxiety among the three AD severity groups Early-onset AD can lead to a poor social adjustment in society and family. Depression and anxiety are influenced by both psychosocial factors and advancing brain damage.
Kaiser et al. [34] USA	**Objective**	To evaluate anxiety in early-onset AD (EOAD) versus late-onset AD (LOAD).
	Study design	Cross-sectional
	Sample	45 Pt (23 with EOAD, Age:57.68; 22 with LOAD, Age:80.32); M:31; F:14; AD Duration (years): 3.09 (EOAD), 3.91 (LOAD); Dementia severity: mild to moderate
	Outcomes	AD criteria: NINCDS-ADRDA
	Assessment	Cognitive abilities assessment: MMSE Anxiety assessment: NPI.
	Results	Higher anxiety in early-onset AD pts than in late-onset AD pts. Association between anxiety, gender, MMSE and separation from caregivers in early-onset AD pts. Association between anxiety

		and psychotic and activating psychiatric symptoms related to dementia progression in late-onset AD pts. Men with early-onset AD are in midlife and have many roles and responsibilities. Thus, early-onset AD has higher impact on the individual than late-onset AD.
Lebedeva et al. [44] Sweden	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To examine the association between depressive symptoms and neuroanatomical changes, brain structure and cerebrospinal fluid AD biomarkers. Cohort observational study. 189 AD Pt with and without depression; M:94; F:95; Age: 71,1; AD Duration (years): n.a.; Dementia severity: n.a. AD criteria: NINCDS-ADRDA and DSM-IV/ICD-10. Cognitive abilities assessment: MMSE Depression assessment: Cornell Scale for Depression in Dementia and Geriatric Depression Scale Association between depression and changes in the temporal and parietal regions, including supramarginal, superior and inferior temporal and fusiform gyri, right posterior cingulate and

		precuneus. Correlation between cortical thickness and t-τ was greater in depressed pts. in precuneus and parahippocampal cortex. More neurodegeneration on limbic structures in depressed AD patients. Disruptions of limbic neural networks can explain depression.
Panegyres et al. [20] Australia	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	Exploring clinical differences between early-onset AD patients and late-onset AD patients. Cross-sectional study. 3747 AD Pt with anxiety or depression (614 with early-onset AD; 3133 with late-onset AD); M:1686; F:2061; Age: 59.3 (early-onset AD) 76.2 (late-onset AD); AD Duration: n.a.; Dementia severity: n.a. AD criteria: McKhann criteria Cognitive abilities assessment: n/a Anxiety and depression assessment: NPI, EQ-5D-3L, and GDS Early-onset AD pts were more likely to have anxiety or depression than late-onset pts. They might be related to dementia severity and more rapid progression.

Tagai et al. [42] Japan	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To investigate how anxiety in AD is related to the structure and function of the brain. Retrospective study 26 Pt with probable AD; M:6; F:20; Age: 74.95; AD Duration: 27 months; Dementia Severity: mild level AD criteria: NINCDS-ADRDA; MRI; SPECT Cognitive function assessment: MMSE; CDR-SB; FAB Anxiety Assessment: Behave-AD Association between anxiety, atrophy in the right precuneus (Pcs) and inferior parietal lobule (IPL) and hyperperfusion of the bilateral anterior cingulate cortex ACC. Pcs, IPL and ACC belong to the fear neurocircuitry and are involved in anxiety disorders. In AD, their degeneration could explain anxiety.
Zahodne et al. [33] USA	**Objective**	To investigate longitudinal associations between functional abilities, cognitive status, and depressive symptoms in AD.

	Study design	Longitudinal study. Pt were assessed prospectively at 6-month intervals for up to 16 years, with an average of 5.5 years.
	Sample	517 Pt with probable AD; M: 222; F: 295; Age: 74.19; AD Duration: n.a.; Dementia severity: mild level
	Outcomes	AD criteria: NINCDS-ADRDA
	Assessment	Cognitive abilities assessment: mMMSE; BDRS Depression Assessment: CUSPAD
	Results	Not worsening of depressive symptoms over AD course. Depressive symptoms predicted functional decline and vice versa. Depression may be reactive to the loss of functional ability, but it is not only a reaction to cognitive decline.
Spalletta et al. [52] Italy	**Objective**	To investigate cognitive progression of AD patients with or without major depressive episode.
	Study design	Longitudinal study.
	Sample	119 newly diagnosed probable AD patients. M:52; F:67; Age:74.7; AD Duration: 2.4 years.; Dementia severity: mild severity
	Outcomes	AD criteria: NINCDS-ADRDA
	Assessment	

		Cognitive abilities assessment: Mental Deterioration Battery, MMSE Depression assessment: a structured interview following modified DSM-IV diagnostic criteria for Major Depressive Episode in AD.
	Results	More MMSE decline in pts with persistent depression, with incident depression over follow-up and in never depressed pts than in pts with recovered depression. depression in AD can be linked to additional cognitive impairment in AD, i.e., frontal planning impairments, that disappear or improve with remission of depression.
van Vliet et al. [40] Holland	**Objective**	To assess neuropsychiatric symptoms in young-onset AD (YO-AD)* and late-onset AD (LO-AD).
	Study design	Prospective cohort study Pt were assessed every 6 months for 2 years
	Sample	221 Pt: 98 with YO-AD (age of onset before 65), 123 with LO-AD; M:99; F:122; Age:70; AD Duration (years): 5.8 (YO-AD) 2.9 (LO-AD); Dementia severity: moderate level
	Outcomes **Assessment**	AD criteria: 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders, Text Revision* (2000) and the Dutch

		consensus guidelines Cognitive abilities assessment: MMSE Depression and anxiety assessment: Neuropsychiatric Inventory
	Results	Depression and anxiety prevalence is lower in young-onset AD than in late-onset AD. Depression is the most prevalent symptom in late-onset AD, and it decreases over time. Depression is less persistent in young-onset AD than in late-onset AD. □ Non-memory phenotype is associated with less atrophy of the medial temporal lobe, so with less symptoms. In oldest patients, contextual factors, i.e., death of a loved one or physical disability, and cerebrovascular diseases may increase depression.
Meynen et al. [39] Netherlands	**Objective** **Study design** **Sample**	To investigate the relationship between depressive state and neuropathological hallmarks of AD. Prospective longitudinal study. Pt were evaluated every 6 months during the last years of their lives 43 Pt with possible or probable AD; M: 10; F: 33; Age:82.8; AD onset: 73.7 years; AD duration: 9.1 years; Age of death: 82.8; Dementia severity: severe level

	Outcomes **Assessment** **Results**	AD criteria: NINCDS-ADRDA; DSM-III-R; Braak stage for tangles Cognitive function assessment: MMSE at baseline; GDS and FAST at 6 months intervals Depression Assessment: CSDD Association between depression and the density of neuritic plaques in the entire cortex, and stronger in the temporal cortex, independently from clinical dementia and AD duration. Decreased cortical metabolism could determine both neuritic plaques and depression. The presence of neuritic plaques in the cortex might contribute, possibly through a toxicity of Aβ-amyloid, to the occurrence of depression. The neuronal damage in the temporal cortex could lead to disinhibition of the HPA-axis, that contribute to depression. Viceversa, depression, associated to HPA hypeactivity and cardiovascular disease, may contribute to AD progress.
Wilson et al. [32] USA	**Objective** **Study design** **Sample**	To characterize change in depressive symptoms before and after the onset of dementia in AD. Longitudinal study 1° subgroup was evaluated every 3-years for a mean of 8 to 9 years.

		2° subgroup: annual evaluation, for a mean of 3 years. 1° group: 357 Pt who developed AD during the study; M:141; F: 216; Age: 82.5 years; Dementia severity: mild level. 2° group: 340 Pt (107 with AD, 81 with MCI, 152 with no cognitive impairment); M:140; F: 200; Age: 81.27 years
	Outcomes **Assessment**	AD criteria: NINCDS-ADRDA Cognitive function assessment: MMSE Depression Assessment: 1° group: CES-D (self-report), v2° group: HDRS (informant report)
	Results	No change in depression during 2 to 3 years of observation after the diagnosis except for a slight decrease in positive affect. □ AD has little systematic effect on depression, since as AD develops, impaired memory and executive control seem to stop the continuity of the depressive state.
Amieva et al. [50] France	**Objective**	To examine the emergence of the first clinical symptoms over a 14-year period of follow-up before the dementia phase of AD.

	Study design	Longitudinal study. Subjects were evaluated at home at the initial visit and at 1, 3, 5, 8, 10, 13, and 15 years.
	Sample	350 AD Pt.; M:243; F:107; Age: 86.2; AD Duration: n.a.; Dementia severity: n.a.
	Outcomes Assessment	AD criteria: NINCDS-ADRDA Cognitive abilities assessment: a battery of tests including MMSE Depression assessment: Center for Epidemiologic Studies-Depression scale (CESD)
	Results	Association between global deficits and depressive symptoms. Depression could be an early reaction to perceived cognitive decline.
Wilson et al. [31] USA	**Objective**	To test the hypothesis that depressive symptoms increase during the prodromal phase of AD.
	Study design	Prospective cohort study.
	Sample	190 Pt with incident AD, M:54; F:136; Age:80.0; AD Duration (years): 3.9; Dementia severity: n.a.
	Outcomes Assessment	AD criteria: NINCDS-ADRDA Cognitive abilities assessment: MMSE Depression assessment: CES-D

	Results	No significant changes in depressive symptoms after the AD diagnosis, although symptoms tended to decrease in women relative to men and in those with a higher premorbid level of openness and a lower premorbid level of agreeableness. Not increasing in depression as mild cognitive impairment developed. Depressive symptoms might influence the relation of the AD pathologic changes to cognition. Depression was associated with sex and personality, and some people experience a depressive reaction to AD.
Tsang et al. [41] Singapore	**Objective** **Study design** **Sample** **Outcomes** **Assessment**	To correlate several glutamatergic measures with chronic anxiety in AD . Prospective longitudinal study 21 Pt with AD (10 with Low Anxiety-LA; 11 with High Anxiety-HA); M: 6; F:15; Age: 77.4; Age at onset: 70.45; Age at death: 79.85; AD duration: 9.4 years Dementia severity: severe cognitive impairment. AD criteria: CERAD scale Cognitive function assessment: MMSE; ADL Anxiety/Depression Assessment: NPI

	Results	Higher binding affinity to glycine recognition sites (GlyRS) in pt with higher anxiety. Association between higher GlyRS affinity, selective reduction of N-methyl-d-aspartate NMDA receptor NR2A density, and elevated anxiety. The development of anxiety in AD can have a neurochemical basis. changes in the NMDA receptor complex can lead to GlyRS hyperfunction that lead to anxiety.
Hashimoto et al. [30] USA	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To investigate the association between anxiety and regional glucose metabolism in AD. Observational, cross-sectional. 41 Pt: M: 35, F: 6; Age: 75.5 years; AD: 2.8 years AD criteria: NINCDS-ADRDA Cognitive abilities assessment: MMSE Anxiety and Depression assessment: NPI. Higher anxiety associated with lower resting metabolism in the bilateral entorhinal cortex, anterior parahippocampal gyrus, and left anterior superior temporal gyrus and insula. Reduced functional activity in the bilateral anterior inferomedial temporal cortex may

		contribute to anxiety in AD, independently from cognitive decline.
Cannon-Spoor et al. [28] USA	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To examine the effect of history of Major Depressive Disorder (MDD) on cognitive performance in AD patients. Multi-site prospective study 43 Pt with AD (22 AD+MDD; 21 AD−MDD); M: 16; F: 27. Age: 69; Age at onset of AD: 66.5; AD duration: 3.35 years Dementia severity: mild to moderate cognitive impairment AD criteria: NINCDS-ADRDA; CDR Cognitive function assessment: test battery consisting of MMSE, WAIS-R, Mattis Initiation/Perseveration subscale, Buschke SRT, Fluency task. Depression Assessment: CADD A history of depression in AD Pt was associated with more severe cognitive deficits. MDD and AD may share some underlying genetic diathesis or may share risk factors. The experience of MDD, particularly if long-lasting or repeated, may result in an insult that increases the

		risk for AD or increases the severity of cognitive symptoms.
Holtzer et al. [29] USA	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To examine the temporal relationship between depressive symptoms, function, and cognitive status in Pt with probable AD. Multicenter cohort study. Pt were followed for up to 14 years and evaluated every 6 months. 536 Pt with probable AD (210 with AD and depression) M: 220; F: 316. Age: 74; AD duration: 4.06 years Dementia severity: mild level of cognitive and functional impairments AD criteria: NINCDS-ADRDA; DSM-III-R Cognitive and functional abilities assessment: 3MS; BDRS Depression Assessment: CUSPAD Depression was associated with functional impairment but not with cognitive impairment. Decline in function, indeed, preceded the first episode of depressive symptoms.

		□ Lower functional activity may be a risk factor for the onset of depressive symptoms in AD.
Milwain et al. [48] UK	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To investigate whether depression may influence the clinical expression of AD, analysing the relationship between cognition, the neuropathological stages of AD and depressive symptoms. Longitudinal study Pt with cognitive impairment were evaluated every 6 months; annually for those without. 89 Pt with AD (48 with depression) M: 39; F: 50; Age: 79.4 Dementia severity: 14.24% Pt in the pre-clinical stage of AD, 21.36% in the intermediate stages of AD, 43.61% in the final stages of AD. AD criteria: Braak stage Cognitive function assessment: CAMCOG Depression Assessment: CAMDEX Depression was associated with a more severe cognitive impairment, but only in intermediate stages of AD. Indeed, depressive symptoms had no impact during the early and advanced stages of AD.

		□ Depressive symptoms may contribute to the cognitive decline of AD Pt. The low prevalence of depression in the final stages of AD may be due to the fact that demented Pt are not able to express the depressive disorder.
Gilley et al. [27] USA	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To evaluate factors related to the development of depressive symptoms in Pt with AD. Longitudinal study. Pt were evaluated at baseline and at up to 4 annual follow-up examinations. 410 Pt with AD, M:136; F: 274; Age: 75.5; Age duration: n.a. Dementia severity: moderate level at the study onset and a severe level at the last evaluation. AD criteria: McKhann criteria Cognitive function assessment: MMSE Depression Assessment: HRS-D + quantitative structured interviews with family members Premorbid neuroticism personality was associated with an increased rate of depressive symptoms in AD Pt. Cognitive impairment was associated with a small reduction in mood symptoms and a modest increase in somatic symptoms.

		□ Decline in mood symptoms with increasing severity of cognitive impairment in Pt with AD it can be explained as the result of the degradation of the ability to experience or express emotion as severity of AD increases.
Wilson et al. [25] USA	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To study the relationship between depressive symptoms, clinical AD, and cognitive impairment. Longitudinal study. 130 elder participants, of whom 51 with probable AD. AD criteria: NINCDS-ADRDA Cognitive abilities assessment: 19 cognitive function tests Depression assessment: Center for Epidemiologic Studies Depression Scale (CES-D) Association of depressive symptoms with clinical AD and cognitive impairment seems to be independent of cortical plaques and tangles. □ Depression-related glucocorticoid effects on neuronal function can contribute to risk of dementia. Depressive symptoms can also contribute to cognitive decline and clinical AD through some psychological mechanism.

Zubenko et al. [26] USA	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To describe the prevalence and clinical features of the major depressive syndrome of AD, comparing Pt with AD to elderly Pt without AD. Comparative study 243 Pt with probable AD. M: 100; F: 143. Age: 78.4; Age at onset of AD: 69.0; Dementia severity: moderate level 151 No-AD Pt. M:70; F: 81; Age: 70.9 AD criteria: NINCDS-ADRDA Cognitive function assessment: MMSE; CDR Depression Assessment: HAM-D; CADD Higher lifetime prevalence of major depression among AD Pt and higher prevalence of MD in AD Pt with severe cognitive impairment. Premorbid major depressive episodes might increase the risk of developing AD; while prevalence of depressive episodes that occurred in the context of AD may be related to neurodegenerative events that contribute to the aetiology of major depression among AD Pt.
Heun et al. [38]	**Objective**	To clarify the relationship between the age at onset of depression in relation to the onset of dementia.

Germany	**Study design**	Longitudinal study
	Sample	57 Pt with AD and MD. M: 18; F: 39. Age: 74.2; Age at onset of AD: 71.7; AD Duration: n.a.
	Outcomes	AD criteria: ICD-10
	Assessment	Cognitive function assessment: MMSE, SIDAM Depression Assessment: CIDI
	Results	Partial correlation between the onset of cognitive impairment and the onset of depression. Depression in AD might not be a symptom of psychological distress, but a symptom of the neurodegenerative process of AD that causes cognitive dysfunction as well.
Chemerinski et al. [46] Argentina	**Objective**	To examine the prevalence and correlates of generalized anxiety disorder (GAD) in AD.
	Study design	Cross-sectional study
	Sample	54 Pt with probable AD (18 with GAD compared with 36 Pt without anxiety disorder). M: 45%; F: 55%; Age: 73.9 AD Duration: 3.15; Dementia severity: mild (AD GAD= 39%; AD control= 72%), moderate (AD GAD= 44%; AD

		control= 22%), severe (AD GAD= 17%; AD control= 6%)
	Outcomes	AD criteria: NINCDS-ADRDA
	Assessment	Cognitive function assessment: MMSE; CDR Anxiety Assessment: DSM-III-R; SCID; SCID-II; HAM-D; HAM-A; Apathy Scale; Bech Mania Scale; PLACS
	Results	GAD in AD was not associated with more severe cognitive impairment. GAD in AD may indicate a subsyndromal depressive state
Haupt, et al. [37] Germany	**Objective**	To study the association between depression and severity of cognitive impairment in AD.
	Study design	Longitudinal study. Pt were followed over 2 years with annual evaluations.
	Sample	78 Pt with AD. M:21; F:57. Age: 74.3; AD Duration: 4.9 years; Age at onset: 69.4; Dementia severity: mild to moderate level
	Outcomes	AD criteria: NINCDS-ADRA; ICD-10
	Assessment	Cognitive function assessment: CAMDEX; CAMCOG; MMSE; GDS; DS; DBS Depression Assessment: DMAS

	Results	Depressive symptoms in AD Pt are in part associated with a greater severity of cognitive impairment. However, depressive symptoms are not prognostically relevant with respect to a lower or higher rate of symptom progression.
Migliorelli et al. [45] Argentina	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To examine the prevalence, risk factors and correlates of depression among patients with AD. Cross-sectional study 103 Pt with probable AD, divided into three groups: major depression (N=24), dysthymia (N=29) and no depression (N=50). M: 27; F: 76. Age: 73.2; AD Duration: 4.3 years; Age at onset: 68.9; Dementia severity: mild (44.29%), moderate (47.38%), severe (14.42%) AD criteria: NINCDS-ADRDA Cognitive function assessment: MMS; WAB; TMT; WCST; BNT; TT; Digit Span Depression Assessment: DSM-III-R; SCID; SCID-II; PSE; FH-RDC; HAM-D; HAM-A; FIM; STC High frequency of depression among Pt with probable AD. Specifically, dysthymia was

		primarily in the early stages of AD, and major depression was distributed across the different stages of the illness. No significant between group differences in the severity of cognitive deficits Dysthymia may be an emotional reaction to the progressive cognitive decline, while major depression may be related to biological factors.
Förstl et al. [47] UK	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To examine the changes in the Locus Coeruleus (LC), Substantia Nigra (SN), basal nucleus of Meynert of AD Pt with and without depression and relate this to clinical features. Prospective study 52 Pt with AD (14 with depression compared with 38 without depression) M: 12; F: 40; Age: 83.2 AD Duration: 8.2 (AD + D group) 7.5 (AD group without depression); Dementia severity: severe cognitive impairment AD criteria: NINCDS-ADRDA Cognitive and functional abilities assessment: MMSE, CAMCOG Depression Assessment: GMSS, CAMDEX In AD Pt with depression, it was observed a lower neuronal count in the locus coeruleus and a higher

		in the basal nucleus of Meynert than AD Pt without depression. There were no differences of the neuron numbers in the SN. Pt with depression showed less cognitive impairment and their verbal skills were better preserved. The observed disproportionate loss of noradrenergic and cholinergic neurons in the LC and basal nucleus of Meynert may represent an important organic substrate of depression in AD.
Lopez et al. [23] USA	**Objective** **Study design** **Sample** **Outcomes** **Assessment**	To evaluate the cognitive functions of patients (Pt) with probable AD and major depression in comparison with Pt with AD and no depression. Longitudinal study. Two evaluations: at baseline and 1-year follow-up. 10 Pt with AD and depression (developed after the onset of symptoms of dementia) compared with 10 nondepressed Pt with AD; M: 4; F:16. Age (years): 67.45; AD Duration (years): 3.2; Dementia severity: Mild level AD criteria: NINCDS-ADRA Cognitive function assessment: MMSE Depression Assessment: DSM-III-R; HAM-D

	Results	No association between depression and cognitive impairment. Pt with AD and depression did not manifest more severe neuropsychological impairments than Pt with AD without depression. Depression does not modify the neuropsychological features and the rate of progression of AD.
Pearlson et al. [24] USA	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To study family history of affective disorder in AD Pt with first-episode depression. Cross-sectional study 112 AD Pt (41 with depression) M:34; F:78; Age: 68,9; AD Duration: n.a.; Dementia severity: severe cognitive impairment AD criteria: NINCDS-ADRDA Cognitive function assessment: MMSE Depression Assessment: DSM-III; FH-RDC (in first and second-degree relatives) The depressed patients had significantly more first and second-degree relatives with depression than did control subjects. Alzheimer's disease as it evolves may interact with an existing genetic vulnerability to affective disorder, which is not expressed until the

		degenerative changes of Alzheimer's disease unfold.
Zweig et al. [22] USA	**Objective** **Study design** **Sample** **Outcomes** **Assessment** **Results**	To evaluate the pathological involvement of the Locus Coeruleus (LC), the Dorsal Raphe Nucleus (DR), and the central superior (raphe) nucleus (CSN) in a series of aged control subjects and AD patients with or without depression. Longitudinal study 22 AD Pt (8 with depression), AD Duration: 7.75; + 12 aged control subjects; Age: 70.7; M:16; F:18; Dementia severity: moderate to severe cognitive impairment AD criteria: post-mortem histological evaluation Cognitive function assessment: MMSE Depression Assessment: DSM-III Compared with control subjects, AD Pt showed higher levels of neuronal loss and higher counts of NFTs, particularly within the LC. Patients with AD complicated by major depression had fewer neurons at the mid level of the LC and at the rostral level of the CSN in comparison with nondepressed patients.

		□ These findings demonstrate histological changes in the brain related to the presence of depression.

Notes. *, young-onset AD is synonymous with early-onset AD and they both indicate AD onset before age 65; 3MS, Modified version of the Mini-Mental State Examination; ACC, Anterior Cingulate Cortex; ACE-R, Addenbrooke's Cognitive Examination Revised; ADL, Activities of Daily Living; BDRS, Blessed Dementia Rating Scale; BPSD, Behavioral and Psychological Symptoms of Dementia; BEHAVE-AD, Behavioural Abnormalities in AD Rating scale; BMS, Bech Mania Scale; BNT, Boston Naming Test; Buschke SRT, Buschke Selective Reminding Task; CADD, Clinical Assessment of Depression in Dementia; CAMCOG, Cambridge Cognition Examination; CAMDEX, Cambridge Examination for Mental Disorders of the Elderly; CIDI, Composite International Diagnostic Interview; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating scale sum of boxes; CERAD, Consortium to Establish a Registry for AD; CES-D, Center for Epidemiologic Studies Depression Scale; CSDD, Cornell scale for depression in dementia; CSF, cerebrospinal fluid; CUSPAD, Columbia University Scale for Psychopathology in Alzheimer's Disease; DBS, Dementia Behaviour Scale; DMAS, Dementia Mood Assessment Scale; DS, Blessed Dementia Scale; EOAD, Early-Onset Alzheimer's Disease; FAB, Frontal Assessment Battery; FAS, Verbal Fluency; FAST, Functional Assessment Staging scale; FH-RDC, Family History Research Diagnostic Criteria; FIM, Functional Independence Measure; GAD, General Anxiety Disorder; GDS, Geriatric Depression Scale; GDS, Global Deterioration Scale; GlyRS, Glycyl-tRNA synthetase; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; HRS-D, Hamilton Rating; Scale for Depression; iADL, instrumental Activity of Daily Living; ICD-10,

International Classification of Diseases Tenth Revision; IPL, Inferior Parietal Lobule; MD, Major Depression; MDRS, Mattis Dementia Rating Scale; LOAD, Late-Onset Alzheimer's Disease; MMSE, Mini Mental State Examination; mMMSE, Modified Mini-Mental State Exam; MRI, Magnetic Resonance Imaging; NIAA, National Institute on Aging-Alzheimer's Association criteria; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria; NMDA, N-methyl-D-aspartate; NPI, Neuropsychiatric Inventory; NPI-Q, Neuropsychiatric Inventory Questionnaire; Pcs, Precuneus; PDC-Dad, Provisional Diagnostic Criteria for Depression of Alzheimer's Disease; PLACS, Pathological Laughing and Crying Scale; PSE, Present State Examination; SCID, Structured Clinical Interview for DSM; SCID-II, Structured Clinical Interview for DSM-III-R-Personality Disorders; SPECT, Single Photon Emission Computed Tomography; SIDAM, Structured Interview for the Diagnosis of Dementia of the Alzheimer's type, Multi-Infarct Dementia and Dementias of other Aetiologies; SRT, Buschke selective reminding test; STC, Social Ties Checklist; TMT, Trail Making Test; TT, Token Test; WAB, Western Aphasia Battery; WAIS-R, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.

Figure 1. Causal factors for anxiety and depression in AD.

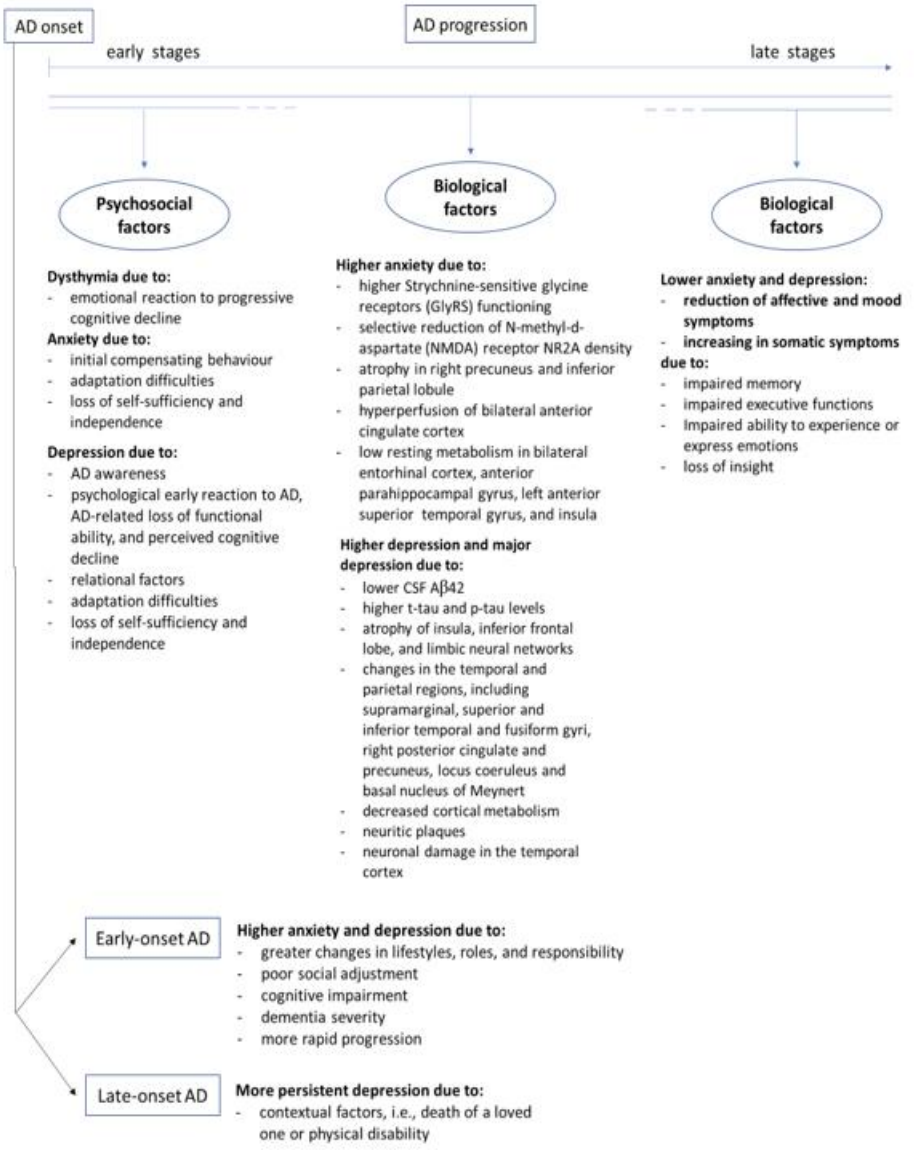
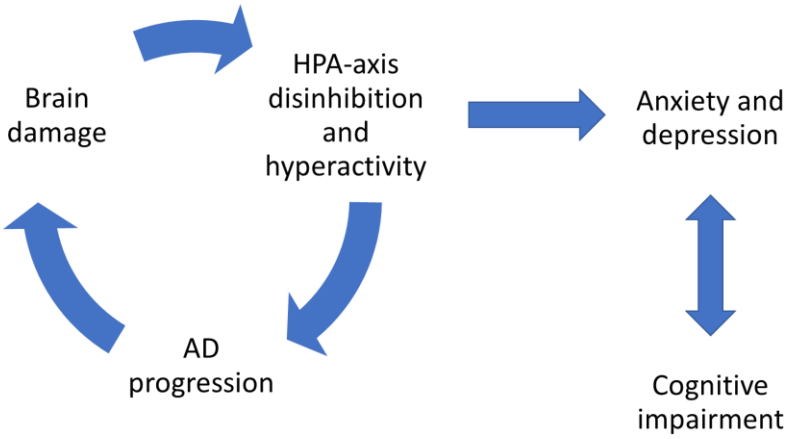


Figure 2. Relationships between anxiety, depression, AD, and cognitive impairment.



4.2 Article n. 2

Demoralization in patients with Mild Cognitive Impairment (MCI): prevalence and association with distress, depression, anxiety, and cognitive functions.

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Submitted.

Abstract

Introduction Mild Cognitive Impairment (MCI) can have a high psychosocial impact on the individual. Difficulties in the adaptation to MCI condition may arise and cause demoralization. This condition of existential distress has not yet been explored in MCI patients.

Objectives The study aimed to investigate the prevalence of demoralization in patients with MCI and its association with distress, depression, anxiety, and cognitive functions.

Methods 45 patients with MCI were assessed for demoralization, distress, depression, anxiety, and cognitive functions using the Italian versions of a set of validated scales.

Results The results showed low levels of demoralization in the sample. The most relevant demoralization sub-dimensions for MCI patients were discouragement and dysphoria. Demoralization was associated with depression, state anxiety, and low cognitive functions. Depression emerged as the demoralization predictor.

Conclusions MCI patients can experience demoralization, especially discouragement and dysphoria, which seems to be related to depression. Psychotherapeutic interventions aimed at identifying new life goals and new coping strategies could alleviate demoralization in MCI patients and favor the search for functional ways of adapting to MCI.

Keywords: MCI, Demoralization, Patients, Distress, Depression, Anxiety

Introduction

Mild Cognitive Impairment (MCI), or minor neurocognitive disorder according to the DSM V (2013), is a clinical condition characterized by a mild dysfunction in one or more cognitive domains (Petersen et al., 1999). This malfunction does not reflect the criteria for the diagnosis of dementia and minimally impacts the activities of daily living (Winblad et al., 2004).

MCI affects 10-15% of the population over the age of 65 (Anderson, 2019) of which 40-60% are at risk of developing Alzheimer's disease (Gillis et al., 2019).

MCI has significant psychosocial implications. Data from literature indicate the presence of neuropsychiatric symptoms in patients with MCI, including apathy (30-40%), agitation and disinhibition (4-35%), psychosis (3-14%), depression and

anxiety (40-50%) (Gallagher et al., 2017). Neuropsychiatric symptoms manifest from the early stages of the disease and commonly get worse with increasing patients' severity of cognitive decline (Trivedi et al., 2013). However, the relationship between neuropsychiatric symptoms and cognitive impairment is not yet clear: psychological symptoms can negatively impact patients' cognitive performance (Dong et al., 2016); on the other hand, psychological distress could be the consequence of cognitive malfunction (Zlot, 1995). Moreover, MCI affects patients' instrumental activities of daily life; this can cause feelings of apathy and a decrease in perceived quality of life (Ginsberg et al., 2019). Finally, the lack of knowledge about the disease and the definition of this illness that often appears vague (Gomersall et al., 2017) can make patients concerned about the progression of the disease, its possible evolution into dementia, and their future (Anderson, 2019).

Thus, MCI can have a high psychosocial impact on the individual, and difficulties in the adaptation to MCI condition may arise. Regarding adaptation concerns, demoralization is a clinical condition that originates from failing in coping with a stressful situation (Clarke & Kissane, 2002). Demoralization is defined as an existential distress syndrome caused by feelings of helplessness, hopelessness, loss of meaning and purpose, sense of failure, discouragement (Kissane et al., 2004; Robinson et al., 2016). Many studies evidenced associations between demoralization and anxiety, depression, suicidal ideation, reduced quality of life, spiritual wellbeing, and loss of dignity (Vehling & Mehnert, 2014; Tecuta et al., 2015; Nanni et al., 2018; Xu et al., 2019; Liu et al., 2019; Zhu et al., 2021).

To our knowledge, the construct of demoralization has mainly been investigated in patients with cancer (An et al., 2018; Tang et al., 2019; Philipp et al., 2019) or long-term neurological diseases such as Parkinson's (Koo et al., 2018; Elfil et al., 2020; Zhu et al., 2021). So, demoralization in patients with MCI has not yet been explored.

Therefore, the present study aimed to investigate the prevalence of demoralization in patients with MCI and its association with distress, depression, anxiety, and cognitive functions.

Methods

Study design and participants

Participants were recruited from April 2019 to April 2021, at Neurology 1 Unit in "Città della Salute e della Scienza" Hospital of Turin, during their hospitalization. They were weekly hospitalized to receive diagnostic exams and visits. Inclusion criteria were aging over 18 and being diagnosed with MCI. The diagnostic criteria for MCI involved: evidence of cognitive decline shown by a score between 23.7 and 27 on the Mini-Mental State Examination (Folstein et al., 1975); preserved daily independence shown by low impairment in the instrumental activities of daily living (scores on Clinical Dementia Rating Scale = .5) (Hughes et al., 1982); and the absence of a diagnosis of dementia, a condition of delirium or mental disorder explaining the cognitive deficits (DSM-V, 2014; Petersen et al., 2004; Petersen et al., 2009).

Exclusion criteria were not speaking Italian fluently and/or taking drugs compromising the ability to provide informed consent and to fill in the scales.

All the participants provided informed consent. The study was approved by "Comitato Etico

Interaziendale A.O.U. San Giovanni Battista di Torino A.O. C.T.O./Maria Adelaide di Torino":

protocol number 0034410, procedure number CS2/1179, date of approval: 29/03/19.

Participants were asked to fill out a sheet collecting their socio-demographic data and a series of self-administered Italian validated scales assessing demoralization, distress, depression, anxiety, and cognitive functions (see Measures section).

Participants were asked to independently fill out the scales, but, if necessary, they received a study researcher's assistance.

Relatively to the statistical power of the study, considering the number of included variables, a sample size greater than 100 participants would ensure good power to the analyzes. Seventy potential participants were identified for the research: of them, 18 were too cognitively compromised and 7 refused to participate in the study. So, the final sample consisted of 45 patients diagnosed with MCI.

Measures

The Italian versions of the following validated scales were used.

Psychological distress assessment

The Demoralization Scale (DS) (Kissane et al., 2004; Costantini et al., 2013) assesses demoralization through 24 items on a 5-point Likert scale, ranging from zero (never) to four (always). The total score of the scale ranges from zero (absence of demoralization) to 96 (maximum level of demoralization). DS includes five subscales: loss of meaning and purpose in life, dysphoria, discouragement, helplessness, and sense of failure. The tool is widely used in literature and has good psychometric properties (Costantini et al., 2013).

The Perceived Stress Scale (PSS) (Cohen et al., 1983; Fossati, 2010) is the most used psychological tool for measuring the perception of distress. This scale is composed of 10 items ranging from zero (never) to four (very often) and is used to assess the distress experienced by the patient in the last month. The total score of the scale ranges from zero (absence of perceived stress) to 40 (severe stress). The person is asked to reflect on how much he assesses stressful situations as uncontrollable and overloaded and how much this affects his psychological well-being.

The State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1989; Spielberger et al., 1983) is a self-assessment questionnaire in the form of a 4-points Likert Scale (1= not at all, 4= very much), consisting of two scales made up of 20 statements

each, that measure state anxiety and trait anxiety, respectively. The total score on the scale ranges from zero to 39 (absence of anxiety). Scores from 40 to 49 indicate mild anxiety, from 50 to 59 moderate anxiety, and >60 severe anxiety.

The Beck Depression Inventory-II (**BDI – II**) (Beck et al., 1996; Sica, C., & Ghisi, M.; 2007) is a self-reporting rating inventory that evaluates the severity of depressive symptoms. It consists of 21 items subdivided into two subscales: the "somatic-affective factor", referring to the loss of pleasure and interests, emotional manifestations, alterations in sleep, appetite, and sexual behavior; and the "cognitive factor" relative to mood, self-esteem, pessimism, and suicidal thoughts. The total score of the scale ranges from 0 (absence of depression) to 63 (severe depression).

Neuropsychological evaluation

The Mini-Mental State Examination (MMSE) (Folstein et al., 1975; Measso et al., 1993) is a widely used test for assessing cognitive ability and decline, especially in elderly subjects. The questionnaire consists of five tasks concerning basic functions: temporal and spatial orientation; memory; attention and calculation; language (including object recognition, repetition of sentences, reading, executing commands, writing); constructive practice (evaluated by hand-copying a drawing).

Rey's 15-words test (RAVLT) (Rey, 1958; Carlesimo et al., 1996) is one of the most used tests to investigate the ability to verbally learn new information. The test consists of a list of 15 words, generally in common use, which is read to the patient. At the end of the list, he must repeat the words he remembers in the order he prefers and takes note. This first part of the test is called immediate recall (IR). After an interval in which the examiner proposes different types of tasks, the patient is asked to recall the words he remembers, without repeating the list. This second part consists of the deferred re-enactment (DR).

The Trail-Making Test (TMT) (Reitan, 1958; Giovagnoli et al., 1996) evaluates visual attention, spatial planning capacity, ability to change tasks, motor skills, and

cognitive flexibility. It is divided into two parts, A and B. In part A the patient must connect (on a sheet with a pencil) the numbers from 1 to 25 in ascending order. He must carry out the task in the shortest possible time. Part B includes numbers and letters presented in random order on the sheet. The patient must perform two tasks simultaneously: he must connect the numbers in ascending order and at the same time the letters in progressive order.

The Frontal Assessment Battery (FAB) (Dubois et al., 2000; Appollonio et al., 2005) is composed of six cognitive and behavioral sub-tests. It is a battery of neuropsychological tests that investigates executive functions. The tasks include phonemic fluency, motor series, response to instructions, prehension behavior, and control of impulsivity.

The Verbal Fluency Test (VFT) (Novelli et al., 1986; Spinnler and Tognoni, 1987) is a language test widely used in the evaluation of language in adults. There are two versions of fluency tests validated for the Italian population:

- Verbal Fluency Test for Letters (VFT_V): the examiner asks the patient to say all the words that come to mind starting with a specific letter. The test is repeated with three different letters. The score reflects the total number of words produced for each letter.
- Semantic Verbal Fluency Test (VFT_S): this second part examines the extension and usability of the lexical content with semantic access. The patient must be uttermost of the words that come to mind that belong to a specific category. The total score is obtained from the sum of all the words spoken.

The Digit Span (DGS) (Monaco et al., 2013; Spinnler and Tognoni, 1987) is a test that evaluates the capacity of short-term memory. It evaluates the span, that is the maximum number of digits that the subject can retain in the working memory and

recall after hearing them verbally. This tool is divided into two parts: digit forward and digit backward.

Statistical Analysis

Descriptive statistics, i.e., means, standard deviations, minimum and maximum scores, and frequencies were calculated to describe each considered variable.

Associations between demoralization and the other considered variables were assessed through Spearman's correlation index, ANOVA, and test t. A linear regression model was performed to identify the significant predictors of demoralization among distress, depression, and anxiety.

All the tests' assumptions were verified, and *p* values equal to or less than .01 or .05 were considered statistically significant. Effect size of statistics, i.e., Cohen's categorization of correlation intensity and adjusted r^2 for regression models were considered.

Statistical analysis was executed using the software SPSS Statistics Version 26.0 (IBM Corp. Armonk, NY, USA).

Results

Sociodemographic characteristics of the sample

The sample consisted of 45 MCI patients, of these 22 were women (48.9%) and 23 were men (51.1%). Most of patients were elder, retired (n= 29, 64.4%), and married (n= 35,77.8%). See Table 1.

Prevalence of demoralization, distress, depression, anxiety, and cognitive functions in the sample.

DS mean total score was low (mean = 21.35, sd = 10.51) and all the participants had scores belonging to the first half of the range (sample DS range = 4-50, possible DS range = 0-96).

"Discouragement" was the DS subscale with higher scores (mean = 7.74, sd = 3.77) (sample "Discouragement" range = 1-15, possible "Discouragement" range = 0-24), followed by "Dysphoria" (mean = 5.12, sd = 3.02) (sample "Dysphoria" range = 0-13, possible "Dysphoria" range = 0-20) and "Sense of failure" (mean = 2.98, sd = 2,63) (sample "Sense of failure" range = 0-10, possible "Sense of failure" range = 0-16).

The sample had a moderate average score of distress and anxiety. Eleven patients (24.4%) had clinically relevant depressive symptomatology.

Sample had a MMSE average score of 24.34 (sd=3.70). Most of the subjects manifested clinically relevant cognitive dysfunctions at RAVLT IR (n=17, 37.8%); RAVLT DR (n=19, 42.2%); FAB (n=28, 62.2%); VFT_S (n=17, 37.8%) and forward DGS (n=9, 20%). See Table 2.

Associations between demoralization and distress, depression, anxiety, and cognitive functions.

DS total score was more associated with BDI total score ($r = .783$; $p \leq .01$) and both BDI "somatic-affective" factor ($r = .740$; $p \leq .01$) and BDI "cognitive" factor ($r = .669$; $p \leq .01$).

"Loss of meaning and purpose in life" DS subscale significantly correlated with BDI total score ($r = .611$; $p \leq .01$) and both BDI "somatic-affective" factor ($r = .564$; $p \leq .01$; $r = .513$; $p \leq .01$) and "BDI "cognitive" factor.

"Dysphoria" DS subscale more correlated with BDI total score ($r = .551$; $p \leq .01$) and with BDI "cognitive" factor ($r = .630$; $p \leq .01$).

"Discouragement" and "Helplessness" DS subscales also more correlated with BDI total score ($r = .560$; $p \leq .01$; $r = .554$; $p \leq .01$).

“Sense of failure” DS subscale significantly correlated with both “state” STAI subscale ($r = .400$; $p \leq .01$) and “trait” STAI subscale ($r = .548$; $p \leq .01$) and with the BDI somatic-affective factor ($r = .422$; $p \leq .01$).

"Sense of failure" DS subscale significantly correlated with MMSE, TMT-A, and B, and FV. "Discouragement" DS subscale significantly correlated with forward DGS. See Table 3.

The regression model evidenced depression as the significant predictor of demoralization.

See Table 4.

Discussion

The present study aimed to investigate the prevalence of demoralization in a sample of 45 patients with MCI and the association of demoralization with distress, depression, anxiety, and cognitive functions.

Concerning the first aim, the average score obtained by the sample on DS suggests low demoralization levels. The clinical subdimensions of demoralization with which participants seem to be more affected are discouragement and dysphoria, albeit at low levels. Discouragement means the presence of a bad mood and feelings of stress, sadness, and loneliness in the patient, together with the perception of feeling trapped by what happened. On the other hand, dysphoria concerns feelings of guilt, irritability, anger, and regret about one's life. These forms of distress may be present in a mild form in MCI patients due to difficulties in coping with the clinical situation that can cause functional and relational limitations, alterations in life roles, and concerns about the illness progression and future. Thus, it could be important to clinically assess these aspects in MCI patients because discouragement could reduce compliance with care and not favor functional adaptation to it, while dysphoria could

lead to a condition of psychological distress that could have a negative impact patient's well-being and exacerbate his symptoms.

Regarding the association between demoralization and the other psychological variables, demoralization was associated with distress and both somatic-affective and cognitive depressive symptoms. In this regard, depression emerged as the demoralization predictor. Therefore, mild depressive symptoms rather than anxious ones could more usually occur in comorbidity with existential distress and a condition of failing in coping in MCI patients. Feelings of loss, which typically are the depressive ones, could be related to the existential crisis opened by MCI, and mood deflection, together with discouragement, prevalently characterize it. Thus, screening and treating MCI patients' depressive symptoms could promote functional coping, prevent the structuring of maladaptive thoughts, and ensure good quality of life.

Concerning anxiety, state anxiety and not trait anxiety was associated with demoralization. However, they both correlated with the sense of failure. Receiving an MCI diagnosis and experiencing MCI symptoms can cause anxiety, that can be related both to the present clinical condition and to its evolution. In this regard, it is conceivable that anxiety cannot favor functional coping, which, in its turn, can lead to demoralization. At the same time, individuals with the tendency to have anxious reactions to stressors could more easily feel a sense of failure when adapting to MCI. Thus, psychotherapeutic work on both anxious states and personality traits could be protective against demoralization in MCI.

Finally, higher demoralization was significantly associated with a reduction in patients' cognitive performances and the sense of failure seems the subdimension of demoralization more related to cognitive functions. In MCI, not feeling able to manage and deal effectively with the disease correlates with poorer attentional, shifting, and verbal performances. Therefore, failing in cognitive tasks can elicit demoralization. On the other hand, a condition of existential distress could reduce

cognitive functioning. In this regard, distress favors cognitive impairment (Katz et al., 2016; Koyanagi et al., 2019), and an increase in blood cortisol in MCI patients, caused by a prolonged stressful condition, appears to be a predictor of MCI progression to dementia (Ávila-Villanueva et al., 2020).

To promote good quality of life in MCI patients it is necessary to assess and satisfy their psychological unmet needs and to treat the psychological symptoms to improve patients' adaptation to illness and prevent possible worsening of their clinical condition. In this regard, psychotherapeutic interventions aimed at identifying new life goals and new coping strategies could help patients in changing their perspectives on the illness and their emotional and existential reactions when dysfunctional, leading them to better accept their condition. This could alleviate demoralization and offer patients new ways of adaptation to adversities (Vehling & Philipp, 2018). Nevertheless, an adaptation of therapeutic strategies is necessary for patients with MCI, but studies are needed on how implement psychotherapy and other psychological interventions into standard care for these patients (Linnemann & Fellgiebel, 2017). Cognitive behavioral psychotherapy also in its "third wave" forms could be effective because of its large effectiveness in different clinical populations (Thoma et al., 2015). Also Meaning-centered psychotherapy could be effective in enhancing sense of meaning (Rosenfeld et al., 2018).

The study has some limitations. First, the small sample size limits the generalizability of the emerged evidence. Then, the cross-sectional design does not allow inferences about the influence of variables on each other. Longitudinal evaluation should be carried out in future studies to clarify the causal relationships between demoralization, psychological symptoms, and cognitive functions in MCI.

Conclusions

MCI patients can experience mild demoralization symptoms, especially discouragement and dysphoria, albeit in a mild form. In MCI, demoralization in MCI

seems to be predicted by depressive symptoms. Psychotherapeutic interventions aimed at identifying new life goals and new coping strategies could alleviate demoralization and depressive symptoms in MCI patients and favor the search for functional ways of adapting to MCI. Cognitive behavioral psychotherapy also in its "third wave" forms and Meaning-centered psychotherapy could be effective, but further studies are needed on this population.

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Tables

Table 1. Socio-demographic characteristics of the sample (N=45)

Socio-demographic characteristics	**N**	**%**
Sex		
Female	22	48.9
Male	23	51.1

Marital Status		
Divorced	3	(6.7)
With cohabiting Partner	2	(4.4)
Married	35	(77.8)
Widow/er	3	(6.7)
Missing	2	(4.4)
Instruction		
Middle School	11	(24.4)
High School	12	(26.7)
Degree	7	(15.6)
Missing	30	(33.3)
Occupational Status		
Employed	8	(17.8)
Retired	29	(64.4)
Unemployed	3	(6.7)
Housewife	3	(6.7)
Missing	2	(4.4)

Caregiver		
Spouse	31	(68.9)
Son/Daughter	10	(22.2)
Partner	1	(2.2)
Missing	3	(6.7)

Notes. N, absolute frequencies; %, percent frequencies.

Table 2. Prevalence of demoralization, distress, depression, anxiety, and cognitive functions in the sample (N = 45).

	Mean	*Sd*	*Min*	*Max*	*Cut-off*	*N*	*%*
DS	*21.35*	*10.51*	*4*	*50*			
Loss of meaning and purpose in life	*2.67*	*2.83*	*0*	*13*			
Dysphoria	*5.12*	*3.02*	*0*	*13*			
Discouragement	*7.74*	*3.77*	*1*	*15*			

Helplessness	*2.86*	*2.63*	*0*	*11*			
Sense of failure	*2.98*	*2.63*	*0*	*10*			
PSS	*15.67*	*6.74*	*2*	*29*			
STAI							
State	*48.26*	*14.04*	*32*	*80*	*0-39*	*15*	*33.3*
					40-49	*12*	*26.7*
					50-59	*6*	*13.3*
					>60	*10*	*22.2*
					missing	*2*	*4.5*
Trait	*46.16*	*19.01*	*0*	*80*	*0-39*	*14*	*31.1*
					40-49	*14*	*31.1*
					50-59	*4*	*8.9*
					>60	*11*	*24.4*
					missing	*2*	*4.5*

BDI – II	*66.35*	*22.86*	*20*	*99*	*<85*	*32*	*71.1*
					85-90	*4*	*8.9*
					91-95	*2*	*4.4*
					>95	*5*	*11.1*
					missing	*2*	*4.5*
Somatic-affective	*67.91*	*19.66*	*20*	*98*	*<85*	*33*	*73.3*
					85-90	*4*	*8.8*
					91-95	*3*	*6.7*
					>95	*3*	*6.7*
					missing	*2*	*4.5*
Cognitive	*71.88*	*20.70*	*40*	*99*	*<85*	*27*	*60.0*
					85-90	*7*	*15.6*
					91-95	*4*	*8.9*
					>95	*5*	*11.0*
					missing	*2*	*4.5*

MMSE	*24.34*	*3.70*	*23.90*	*27.00*			
RAVLT IR	*29.04*	*11.64*	*0*	*57.0*			
0						*17*	*37.8*
1						*2*	*4.4*
2						*11*	*24.4*
3						*5*	*11.1*
4						*4*	*8.9*
missing						*6*	*13.4*
RAVLT DR	*5.22*	*3.80*	*.0*	*14.1*			
0						*19*	*42.2*
1						*2*	*4.4*
2						*6*	*13.3*
3						*5*	*11.1*
4						*6*	*13.3*
missing						*7*	*15.7*

TMT A	*72.74*	*59.92*	*-.74*	*273.87*			
0						*12*	*26.7*
1						*5*	*11.1*
2						*8*	*17.8*
3						*3*	*6.7*
4						*13*	*28.9*
missing						*4*	*8.8*
TMT B	*176.86*	*125.20*	*.00*	*500.00*			
0						*8*	*17.8*
1						*8*	*17.8*
2						*2*	*4.4*
3						*6*	*13.3*
4						*11*	*24.4*
missing						*10*	*22.3*
TMT B - A	*104.12*	*82.31*	*-.74*	*226.13*			

FAB	*12.19*	*2.73*	*4.4*	*18.0*			
0						*28*	*62.2*
1						*5*	*11.1*
2						*5*	*11.1*
3						*0*	*0*
4						*3*	*6.7*
missing						*4*	*8.9*
VFT FON	*25.40*	*11.58*	*5.00*	*61.60*			
0						*10*	*22.2*
1						*8*	*17.8*
2						*6*	*13.3*
3						*5*	*11.1*
4						*14*	*31.1*
missing						*2*	*4.5*

VFT SEM	*23.01*	*15.40*	*.00*	*60.00*			
0						*17*	*37.8*
1						*4*	*8.9*
2						*5*	*11.1*
3						*4*	*8.9*
4						*8*	*17.8*
missing						*7*	*15.5*
DGS forward	*5.47*	*2.49*	*.00*	*16.75*			
0						*6*	*13.3*
1						*3*	*6.7*
2						*9*	*20.0*
3						*6*	*13.3*
4						*9*	*20.0*
missing						*12*	*26.7*

DGS backward	*3.19*	*1.23*	*.00*	*6.99*			
0						*8*	*17.8*
1						*10*	*22.2*
2						*7*	*15.6*
3						*5*	*11.1*
4						*2*	*4.4*
missing						*13*	*28.9*

Notes. sd, standard deviation; min, the lowest score in the sample; max, the highest score in the sample; N, absolute frequencies; %, percent frequencies; DS, Demoralization Scale; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; cut off STAI:
0-39 absence of anxiety, 40-49 mild anxiety, 50-59 moderate anxiety, >60 severe anxiety; cut off BDI: they are relative to corrected BDI scores: <85 absence of depression, 85-90 borderline depression, 91-95 moderate depressive symptoms, >95 severe depression; MMSE, Mini-Mental State Examination; RAVLT IR, Rey's 15-Words test Immediate Recall; RAVLT DR, Rey's 15-Words test Deferred Recall; TMT A, Trail Making Test part A; TMT B, Trail Making Test part B; FAB, Frontal Assessment Battery; FV, Verbal Fluency Test, FON, phonemic, SEM, semantic; DGS, Digit Span; Equivalent Scores, 0:deficient; 1:borderline; 2-3: lower average; 4: higher average.

Table 3. Associations between demoralization and distress, depression, anxiety, and cognitive functions (N = 45).

	DS Total score r	DS Loss of meaning and purpose in life r	DS Dysphoria r	DS Discouragement r	DS Helplessness r	DS Sense of failure r
PSS	.394**	-	.355*	.310*	.432**	-
STAI State	-	-	-	-	-	.400**
STAI Trait	.318*	-	-	-	-	.548**

BDI - II	.783**	.611**	.551**	.560**	.554**	.365*
BDI - II Somatic-affective	.740**	.564**	.480**	.555**	.530**	.422**
BDI - II Cognitive	.669**	.513**	.630**	.481**	.427**	-
MMSE	-	-	-	-	-	*-.345**
RAVLT IR	-	-	-	-	-	-
TMT A	-	-	-	-	-	*.431***
TMT B	-	-	-	-	-	*.476***
VFT SEM	-	-	-	-	-	*-.349**

DGS forward	-	-	-	*.423**	-	-

**, $p \leq .01$

*, $p \leq .05$

The table shows only significant correlations; r, Spearman's correlation index; DS, Demoralization Scale, PSS, Perceived Stress Scale; STAI State-Trait Anxiety Inventory; BDI Beck Depression Inventory; MMSE, Mini-Mental State Examination; RAVLT IR, Rey's 15-Words test IR Immediate Recall; TMT A, Trail Making Test A; TMT B, Trail Making Test B, FV SEM, Verbal Fluency Test Semantic; DGS, Digit Span. Intensity of correlations: r < .4, low; 3 < r < 6, mild; r > 6, high.

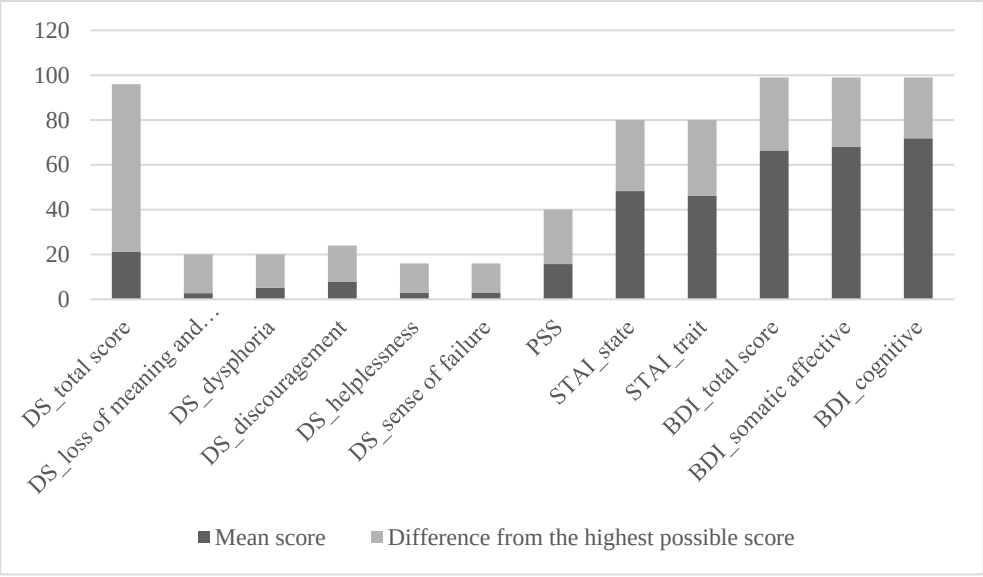
Table 4. Demoralization significant predictors (N = 45).

Dependent Variable: Demoralization total score					
Independent Variables	B	SE	β	*p-value*	CI
Constant	-2.300	3.934		.000	-23.17 - -3.9
Depression (BDI-II)	.363	.055	.780	.007	.48 – 1.40

Notes. Adjusted R^2, .595. Adjusted R^2, .700; B, unstandardized regression coefficient; SE, standard error; β, beta coefficient; CI, confidence interval BDI-II, Beck Depression Inventory-II version.

Figures

Figure 1. Patients' levels of demoralization, distress, anxiety, and depression (N = 45).



Notes. DS, Demoralization Scale; PSS, Perceived Stress Scale; STAI, State Trait Anxiety Inventory; BDI, Beck Depression Inventory.

4.3 Article n. 3

Psychological distress in young adults after multiple sclerosis diagnosis.

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Submitted.

Abstract

Background The diagnosis of multiple sclerosis (MS) can be a critical and stressful event. After diagnosis patients can experience an existential crisis and are required to adapt to their new medical condition. Thus, they can develop psychological symptoms.

Aims The study aimed to assess distress, post-traumatic stress, anxiety, depression, and demoralization in MS young adults who have been diagnosed for up to six months; to explore the association between these forms of psychological distress and coping, quality of life, fatigue, and cognitive impairment; and to longitudinally test if psychological distress varied or less during the following year.

Methods 55 patients with relapsing-remitting MS were asked for three evaluations: within six months after the diagnosis for T0, at six months after T0, and one year after T0. A set of validated rating scales measuring distress, anxiety, depression, demoralization, coping, quality of life, fatigue, and cognitive functioning was administered to patients.

Results The sample had moderate stress levels, moderate demoralization, and low depression. Almost on third of participants had post-traumatic symptoms and anxiety. 21.8% of patients had severe depression. These psychological symptoms were significantly associated with coping, fatigue, quality of life, and cognitive functions, and remained unchanged during the follow-up.

Conclusions The MS diagnostic communication is a significant event to which patients could react with different forms of psychological distress, especially during young adulthood. Psychological interventions could be effective in promoting functional coping and regulating symptoms. Furthermore, caring the communication and supporting patients after diagnosis can contribute to their psychological well-being.

Keywords

Multiple sclerosis, diagnosis, diagnostic communication, psychological distress, young adult.

Introduction

Multiple sclerosis (MS) is a neurodegenerative disease. It is idiopathic, chronic, and inflammatory, and it is characterized by sclerotization that occurs during the disease progression (Lazibat et al., 2018). Relapsing-remitting multiple sclerosis (RR-MS), one of MS's most frequent subtypes, consists of episodes of acute worsening with total or partial recovery (Klineova & Lublin, 2018).

Due to MS, patients can suffer from several symptoms, such as fatigue, pain, sensory and motor disorders, bowel, bladder, and sexual disturbances, and cognitive impairment (Calandri et al., 2019). Furthermore, for the fact of being a chronic, symptomatic, and unpredictable disease, with no resolutive treatments, MS has a significant impact on the individual, reducing his quality of life and causing psychological distress (Calandri et al., 2019; Topcu et al., 2020).

Thus, MS diagnostic communication can be a critical and stressful event for patients (Kamm et al., 2020). In the phase immediately following the diagnostic communication, patients gain awareness and information about the disease and must adapt to their new clinical condition. So, they can experience an existential crisis opening to changes and alteration of previous equilibria. Moreover, most patients with RR-MS are diagnosed during young adulthood, and diagnosis can negatively impact a life moment characterized by planning and long-term decisions to take (George et al., 2016). The period surrounding MS diagnosis is undoubtedly emotionally intense (Castillo-Triviño et al., 2022). After the disclosure of the diagnosis, fear, distress, anxiety, and depression may appear and the adaptation to the disease can be challenging (Topcu et al., 2020; Gajofatto et al., 2019; Calandri et al., 2019; Hanna & Strober, 2020).

To our knowledge, to date, only a few studies provided evidence on the psychological adaptation to the MS diagnosis during the early stages of the disease. Calandri and colleagues (2019), Gajofatto and colleagues (2019), and Graziano and

colleagues (2020) cross-sectionally studied adjustment in MS young adults or adults who received the diagnosis of MS in the three previous years, assessing psychological symptoms, patients' satisfaction, and self-efficacy. Finally, McNicholas and colleagues (2021) cross-sectionally assessed anxiety, depression, and fatigue in MS patients up to 12 months after diagnosis and MS patients with a mean MS duration of 17 years (range 3-47).

Therefore, to provide further evidence on the theme, this study firstly aimed to assess distress, post-traumatic stress, anxiety, depression, and demoralization in RR-MS young adults who received the diagnosis at the most for six months. Secondly, it aimed to explore the association between these forms of psychological distress and coping, quality of life, fatigue, and cognitive impairment. Finally, it aimed to longitudinally test if psychological distress varied or less during the following year.

Methods

Study design and participants

The sample was recruited between January 2020 and July 2022 at the Multiple Sclerosis Centre of the Neurology Unit of "Città della Salute e della Scienza" Hospital in Turin.

The inclusion criteria were having an age between 18 and 60 years old, understanding the Italian language, having received a diagnosis of relapsing-remitting multiple sclerosis (RR-MS) in the previous six months, having started the medical therapies, and having a score on the Expanded Disability Status Scale ≤ 5 (Kurtzke, 1983). Patients with any comorbid psychiatric disorder, severe organic syndrome, or cognitive impairment which prevented giving informed consent or

compromised participation in the research were excluded. These conditions were evaluated by patient's referring physician on the basis of the clinical sessions held with the patient.

Eighty-seven patients were invited to participate in the research by their attending physician during their neurological follow-up visits. 25 of them did not meet the inclusion criteria and 8 of them declined participation in the study. The final sample consisted of 55 patients.

The study design was longitudinal. Patients were asked for three evaluations over the course of 12 months: first evaluation (T0) within six months after the diagnosis, second evaluation (T1) six months after T0, and last evaluation (T2) one year after T0. The evaluations were offered to patients on the same days as their neurological follow-up visits and/or pharmacological therapies were scheduled, so as not to have patients come to the center on purpose.

During the first evaluation, patients' socio-demographic data were collected, and patients were administered with a set of validated rating scales measuring distress, anxiety, depression, demoralization, coping, quality of life, and fatigue, and with a neuropsychological battery assessing the cognitive functioning (see Measures section). The same scales and battery were proposed again in the same sequence at T1 and T2.

Relatively to the statistical power of the study, considering the number of included variables, a sample size greater than 150 participants would ensure good power to the analyzes. Fifty-five patients received the first evaluation. Twenty-one patients stopped their participation after the first evaluation and 15 patients did not receive the third evaluation due to unavailability; 9 patients did not participate in the second evaluation due to contingent limitations but received the third. Thus, 25 patients received the second evaluation and 19 the third (see Figure 1)

Written informed consent was obtained from all participants and the present research was approved by "Comitato Etico Interaziendale A.O.U. San Giovanni Battista di Torino A.O. C.T.O./Maria Adelaide di Torino": protocol number 0034410, procedure number CS2/1179, date of approval: 29/03/19. The authors affirm that the research is in conformance with the Declaration of Helsinki.

Measures

The Perceived Stress Scale (PSS) (Cohen et al., 1983; Fossati, 2010) measures patients' perception of circumstances of their life as stressful (Cohen et al., 1983). It consists of 10 items on a five-point Likert scale, from 0 (never) to 4 (very often). Three score ranges were established to be associated with three different levels of perceived stress: 0-13: low stress; 14-26: moderate stress; 27-40: high stress.

The Impact of Event Scale-Revised (IES-R) (Weiss et al, 1997; Giannantonio, 2003) measures stress after traumatic events and consists of three subscales that measure avoidance, hyperarousal, and intrusiveness. For the research, the event to consider was the communication of the diagnosis. It has 22 items on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The cut-off was 33 for both males and females.

The State-Trait Anxiety Inventory (STAI) (Spielberger, 1970; Pedrabissi & Santinello, 1989) is a self-evaluation questionnaire, consisting of two subscales: STAI Y1 assesses state anxiety, that is anxiety as a symptom; STAI Y2 evaluates anxiety as a habitual style of reacting to external stimuli. Each subscale has 20 items on a four-point Likert scale ranging from 4 (very much) to 1 (not at all). Different levels of anxiety are distinguished, where a higher score is associated with greater

anxiety: 0-39: no anxiety; 40-49: mild anxiety; 50-59: moderate anxiety; >60 severe anxiety. The cut-off for both subscales was 40 for males and females.

The Beck Depression Inventory-II (BDI-II) (Beck et al., 1961; Ghisi et al., 2006) is specifically designed to assess depressive symptoms. It consists of 21 items on a four-point Likert scale, each describing a possible specific manifestation of depression that occurred in the last two weeks. Six levels of depression can be detected: 0-10: minimal; 11-16: mild; 17-20: borderline; 21-30: moderate; 31-40: severe; 40: extreme.

The Demoralization Scale (DS) (Kissane et al., 2004; Costantini et al., 2013) is a scale assessing demoralization and is subdivided into 5 subscales: loss of meaning and purpose in life, dysphoria, discouragement, powerlessness, and sense of failure. The scale has 24 items on a 5-point Likert scale ranging from 0(never) to 4 (always). The cut-off was 30 for both males and females. Greater severity and frequency of the state experienced are correlated with higher ratings.

The Coping Orientation to Problems Experienced – New Italian Version (COPE-NVI) (Carver et al., 1989; Sica et al., 2008) is specifically designed to investigate coping. It is a 60-item questionnaire, which measures five different coping strategies: social support, avoidance strategies, positive attitude, problem orientation, and transcendent orientation. Each subscale had its cut-off score. The items are on a four-point Likert scale ranging from 1 (I typically do not do it) to 4 (I almost always do it).

The Multiple Sclerosis Quality of Life – 29 (MSQOL-29) (Rosato et al., 2016) is a questionnaire that evaluates the quality of life of MS patients. It specifically investigates physical function, pain, emotional well-being, energy, cognitive function, health stress, sexual function, health change, social function, health

perception, and general quality of life. Scores are determined by two indices, the Physical Component Summary, and the Mental Component Summary index, which are formed from the sum of the averages of the items of the subscales. It has 29 items on a four-to-six-Likert scale, and two versions, for females and males.

The Fatigue Scale for Motor and Cognitive functions (FSMC) (Penner et al., 2009) measures cognitive and physical fatigue in MS patients. It has 20 items on a 5-point Likert scale ranging from 1 (it never happens) to 5 (it always happens). Different levels of fatigue can be identified: < 43: no fatigue; > 43: mild fatigue; > 53: moderate fatigue; > 63: severe fatigue. The cut-off for total fatigue was 43, while it was 22 for the cognitive and physical subscales.

The Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) (Cognitive Function Study Group-American Multiple Sclerosis Society; Rao et al., 1991) is specifically used to determine the degree of cognitive impairment in MS patients. It consists of seven tests designed to measure executive functions, attention, and memory: Selective Reminding Test (SRT), 10/36-Spatial Recall Test (SPART), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), Delayed Recall of the Selective Reminding Test (SPART-D), Delayed Recall of the 10/36-Spatial Recall Test, and Word List Generation (WLG; WORD).

Statistical analysis

Sociodemographic variables and test scores were initially assessed using descriptive statistics, including frequencies, percentages, averages, and standard deviation.

The Spearman correlation index was used to observe the associations of stress, anxiety, depression, and demoralization with coping, quality of life, and fatigue at

T0. Then, the same index was used to assess the associations of stress, anxiety, depression, and demoralization with cognitive functioning.

Finally, a repeated measures ANOVA was performed to investigate possible variations of the levels of stress, anxiety, depression, and demoralization among T0, T1, and T2.

All the assumptions of the tests were verified and *a p-value* ≤ 0.05 was considered statistically significant. Effect size of statistics, i.e., Cohen's categorization of correlation intensity, was considered. Statistical analyses were performed using SPSS version 25 (Statistical Package for Social Sciences, Chicago, IL, USA).

Results

Socio-demographic characteristics of the sample

The final sample consisted of 55 patients, with an average age of 34.87 years (sd = 11.73, range 18-60 years). Most of the sample was female (n = 31, 56.4%), married (n = 14, 25.5%), employed (n = 25, 45.5%), and with 13 years of schooling (n = 23, 41.8%). See Table 1.

Prevalence of psychological distress in the sample

The average score of the sample at the PSS was 17.71 (sd = 8.66) and most of the patients had moderate stress levels (n = 24, 43.6%).

The sample's average score at IES-R was 26.28 (sd = 18.75). Most of the patients (n = 40, 72.8%) did not have post-traumatic symptomatology, but 15 patients (27.2%) had post-traumatic symptoms.
The sample's mean score was 39.29 (sd = 11.54) at STAI Y1 and 43.02 (sd = 13.86) at STAI Y2. Almost one-third of the sample had state anxious symptoms (n = 25, 45.5%) and trait anxiety (n = 29, 52.7%).
The average score of the sample at the BDI-II was 12.08 (sd = 9.33). Most of the patients had normal mood (n = 32, 58.2%), but 16 patients (29.1%) reported severe depression.
The sample's average score at the DS was 27.18 (sd = 18.96). The DS subscales with the higher mean scores were "Disheartenment" with 8.62 (sd = 5.57) and "Dysphoria" with 6.40 (sd = 4.33). See Table 2.
Table 2 presented the prevalence data of the sample also at T1 and T2. No significant differences emerged between T0, T1 and T2 mean scores for all the scales. See Table 2.

Association between psychological distress and coping, fatigue, quality of life, and cognitive functions

All the investigated forms of psychological distress were significantly associated with coping, fatigue, quality of life, and with cognitive functions, with the following exceptions: demoralization and trait anxiety showed no significant correlations with cognitive functions; only depression was associated with "physical functioning" quality of life subscale.

The highest correlations were between PSS and "emotional wellbeing" MSQOL-29 subscale; between STAI Y1 and Mental Composite Score (MCS), "emotional wellbeing" and "health stress" MSQOL-29 subscales; between STAI Y2 and

"avoidance" COPE-NVI subscale, "emotional wellbeing" and "health stress" MSQOL-29 subscales.

BDI total score showed high correlations with "avoidance" COPE-NVI subscale, with cognitive fatigue, and with MCS, "emotional wellbeing", "energy", "cognitive function", "health stress" and "overall quality of life" MSQOL-29 subscales.

DS correlated highly with "avoidance" COPE-NVI, and with MCS, "emotional wellbeing", "health stress" and "overall quality of life" MSQOL-29 subscales (see Table 3).

Discussion

Data indicated in the sample different forms of psychological distress, such as distress, post-traumatic symptoms, anxiety, depression, and demoralization. This psychological suffering was detected in the period immediately following the diagnostic communication. The reception of the MS diagnosis can be lived as an adverse event opening a crisis that compromises personal balance and forces the patient to the adaptation to the new medical condition (Bonino, 2019). Diagnostic communication seems to be significant information to which patients' body-mind system reacts. Stress and anxiety could represent the activation in reaction to a new situation and possible threats to safety, health, and functioning to which the patient is exposed. Post-traumatic symptoms could arise when the patient struggles to integrate this significant information into his emotional and memory circuits, and the received information continues to impact him. Depression and demoralization could signal possible shortcomings and losses that the patient lives and the failure in coping with the new medical condition. Difficulties in integrating the perturbations that the MS diagnostic communication generates, and in accepting the disease and its related

aspects could, therefore, contribute to the onset and exacerbation of the psychological symptoms.

Moreover, most of the participants were young adults. Thus, receiving an MS diagnosis during young adulthood could be highly distressing because the impact of MS on work, life planning, activities, and social and familiar area can be stronger (Lorefice et al., 2017).

Offering psychological interventions to patients with psychological symptoms could be effective in promoting functional coping, regulating symptoms, and helping the person to better understand why and how the diagnostic communication has impacted his/her existential balance and to modify subjective dysfunctional reactions and cognitive, emotional, and behavioral functioning (Borghi et al., 2018). Furthermore, taking care of the psycho-social aspects of communication and adequately supporting patients after giving them the diagnosis are important duties of all members of the healthcare team that contribute to supporting patients' psychological well-being (Alroughani, 2015).

By monitoring patients during the first year following diagnosis, it was observed that the psychological symptoms remained almost unchanged. Probably, receiving an MS diagnosis during young adulthood solicits a complex adaptation process that requires time. Thus, psychological symptoms should not be disregarded and underestimated because they signal patients' difficulties that must be assessed and treated. Longitudinal studies with longer-term symptom monitoring could provide precious evidence of their variation concerning the MS course. Moreover, further research on the psychological interventions received by patients could help in providing adequate treatments to MS patients.

Psychological distress was associated with coping, fatigue, quality of life, and cognitive functions. Avoidance coping strategy was strongly related to distress,

probably because it prevents the patient to manage the difficulties of adaptation. Distress was also related to higher fatigue and worse quality of life. The worsening of patients' psychological well-being could contribute to increase fatigue (Zielinski et al., 2019) and reduce patients' overall well-being (Yalachkov et al., 2019). This evidence confirms the relevance of implementing distress management interventions that could reduce the impact of distress on patients' physical and general well-being (Anagnostouli et al., 2019).

Finally, psychological distress, particularly anxiety and depression, was associated with worse attentive and memory objective capacities, higher cognitive fatigue, and lower perceived cognitive functioning. Worse cognitive abilities could elicit distress. On the other hand, distress could play a role in MS progression and patients' perception of MS symptoms. Further studies might contribute to the explanation of these associations.

The study has some limitations. The sample size was small, and the number of participants has been reduced during the follow-up. This limited the possibilities of the formal analysis, e.g., the analysis of the role of the socio-demographic data in distress. Finally, the collection of biological or neuroimaging data on patients' diseases, e.g., data on RR-SM from the magnetic resonance or blood cortisol levels was not possible due to instrumental and economically limited resources. Better exploring the social and biological aspects of distress in SM patients could contribute to a better understanding of it.

Conclusions

Diagnostic communication is a significant event to which patients could react with different forms of psychological distress, such as distress, post-traumatic symptoms,

anxiety, depression, and demoralization, that can remain almost unchanged during the first year following diagnosis.

Difficulties in integrating the perturbations that the MS diagnostic communication generates, and in accepting the disease and its related aspects could contribute to the onset and exacerbation of the psychological symptoms, especially if the diagnosis is received during young adulthood.

Offering psychological interventions to patients with psychological symptoms could be effective in promoting functional coping and regulating symptoms. Furthermore, taking care of the psycho-social aspects of communication and adequately supporting patients after diagnosis contributes to preserving patients' psychological well-being.

Finally, psychological distress was associated with dysfunctional coping, higher fatigue, worse quality of life, and worse cognitive functions. This evidence confirmed the relevance of implementing distress management interventions that could reduce the impact of distress on patients' general well-being.

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Tables

Table 1. Socio-demographic characteristics of the sample (N = 55)

Characteristic	n **(%)**
Age	34.87±11.73
Sex	
Male	24 (43.6)
Female	31 (56.4)
Marital status	
Single	9 (16.4)
Married	14 (25.5)
Divorced	2 (3.6)
Cohabiting partner	12 (21.8)
Not-cohabiting partner	6 (10.9)
Missing	12 (21.8)
Education (years)	
< 10	5 (9.1)
10-15	31 (56.3)

> 15	17 (30.8)
Missing	2 (3.6)
Profession	
Employed	25 (45.5)
Unemployed	9 (16.4)
Retired	1 (1.8)
Housewife	1 (1.8)
Student	6 (10.9)
Precarious	1 (1.8)
Missing	12 (21.8)
Caregiver	
Spouse	10 (18.2)
Partner	10 (18.2)
Other relatives	11 (20)
Missing	24 (43.6)

Notes. N, absolute frequencies; %, percent frequencies.

Table 2. Prevalence of psychological distress in the sample.

	T0 **N = 55** **mean ± sd** **n (%)**	**T1** **N = 25** **mean ± sd** **n (%)**	**T2** **N = 19** **mean ± sd** **n (%)**
PSS	17.71 ± 8.66	18.06 ± 6.25	19.20 ± 8.16
<13	22 (40)	9 (36)	2 (10.5)
14-26	24 (43.6)	15 (60)	13 (68.5)
27-40	9 (16.4)	1 (4)	4 (21)
IES-R			
Total	26.28 ± 18.75	25.12 ± 15.99	27.90 ± 25.14
< 33	40 (72.8)	19 (76)	11 (57.9)
> 33	15 (27.2)	6 (24)	8 (42.1)
Total mean	3.62 ± 2.62	3.40 ± 2.03	3.82 ± 3.57
Avoidance mean	1.27 ± 0.90	0.87 ± 0.49	1.20 ± 1.16
Intrusiveness mean	1.30 ± 1.03	1.45 ± 0.93	1.45 ± 1.36
Hyperarousal mean	1.07 ± 0.99	1.07 ± 0.99	1.17 ± 1.25
STAI			
Stai Y1	39.29 ± 11.54	40.47 ± 15.26	40.00 ± 10.98

< 40	30 (54.5)	15 (60)	11 (57.9)
> 40	25 (45.5)	10 (40)	8 (42.1)
Stai Y2	43.02 ± 13.86	41.29 ± 11.23	43.00 ± 13.83
< 40	26 (47.3)	12 (48)	8 (42.1)
> 40	29 (52.7)	13 (52)	11 (57.9)
BDI-II			
Total	69.22 ± 27.31	61.24 ± 28.94	65.80 ± 23.01
<85	32 (58.2)	20 (80)	13 (68.5)
85-90	4 (7.3)	1 (4)	2 (10.5)
91-95	3 (5.4)	1 (4)	2 (10.5)
>95	16 (29.1)	3 (12)	2 (10.5)
Somatic	70 ± 25.41	60.82 ± 26.02	66.20 ± 24.51
<85	31 (56.4)	21 (84)	13 (68.5)
85-90	8 (14.5)	3 (12)	2 (10.5)
91-95	3 (5.5)	-	-
>95	13 (23.6)	1 (4)	4 (21)
Cognitive	74.66 ± 21.22	69.12 ± 23.91	72.10 ± 19.95
<85	31 (56.4)	15 (60)	11 (58)
85-90	4 (7.3)	-	4 (21)

91-95	5 (9)	5 (20)	2 (10.5)
>95	15 (27.3)	5 (20)	2 (10.5)
DS			
Total	27.18 ± 18.96	26.76 ± 17.44	24.40 ± 20.23
Loss of meaning	3.07 ± 4.10	2.47 ± 3.26	2.50 ± 3.78
Dysphoria	6.40 ± 4.33	6.29 ± 5.14	5.40 ± 4.30
Disheartenment	8.62 ± 5.57	8.88 ± 5.44	7.80 ± 6.63
Helplessness	3.98 ± 3.80	4.24 ± 4.10	3.90 ± 3.87
Sense of failure	4.98 ± 3.53	4.88 ± 2.80	4.80 ± 3.39

Notes. Sd, standard deviation; n, absolute frequencies; %, percent frequencies; PSS, Perceived Stress Scale; STAI Y1-Y2, State-Trait Anxiety Inventory; BDI-II, Beck Depression Inventory; DS, Demoralization Scale; IES-R, Impact of Event Scale-Revised.

Table 3. Association between psychological distress and coping, fatigue, QOL and cognitive functions

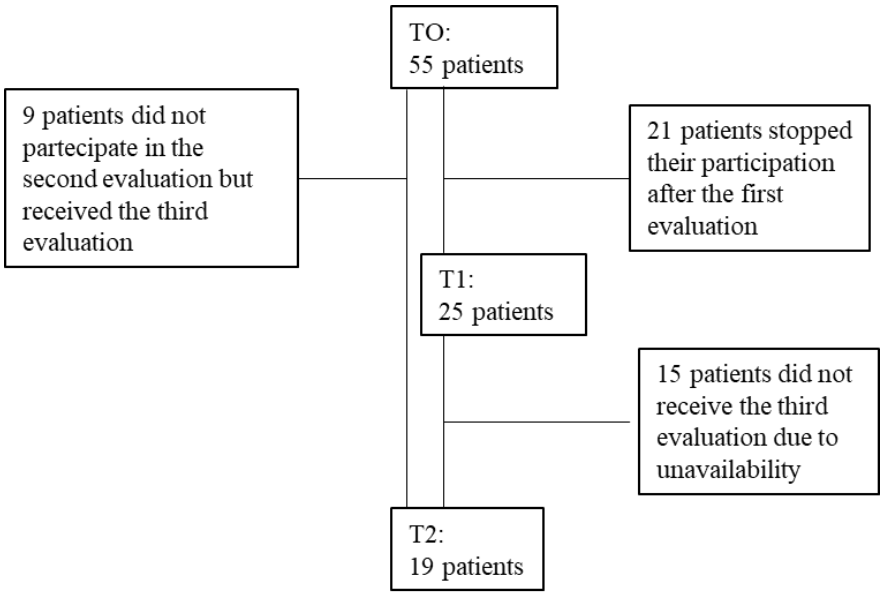
	PSS	STAI Y1	STAI Y2	BDI Total score	DS Total score	IES-R Total score
COPE-NVI						
Social support	.35*	-	.44**	-	.45**	.38*
Avoidance	.67*	.56**	.72**	.71**	.72**	.62**
Positive attitude	-	-.32*	-.33*	-	-	-
Problem orientation	-	-	-	-	-	-
FSMC						
Total score	.54**	.47**	.49**	.68**	.57**	.49**
Cognitive fatigue	.56**	.44**	.51**	.71**	.61**	.49**
Physical fatigue	.50**	.46**	.43**	.63**	.50**	.46**
MSQOL-29						
PCS	-.50**	-.51**	-.52**	-.64**	-.63**	-.35*
MCS	-.68**	-.72**	-.68**	-.83**	-.79**	-.47**
physical functioning	-	-	-	-.35*	-	-
pain	-.35*	-.45**	-.31*	-.49**	-.30*	-.36*
emotional wellbeing						

energy	-.78**	-.72**	-.79**	-.79**	-.83**	-.46**
cognitive	-.56**	-.48**	-.53**	-.70**	-.60**	-
function	-.54**	-.49**	-.55**	-.70**	-.63**	-.38*
health stress	-.69**	-.80**	-.77**	-.81**	-.87**	-.54**
sexual function	-.49**	-.54**	-.48**	-.62**	-.57**	-.40*
social function	-.54**	-.68**	-.48**	-.64**	-.57**	-.40*
health perception	-.36*	-	-.36*	-.49**	-.47**	-
overall quality of life	-.59**	-.64**	-.64**	-.72**	-.75**	-.34*
SDMT	-	-.31*	-	-.37*	-	-
SPART-D	-	-.39*	-	-.31*	-	-
PASAT 2	-.35*	-	-	-	-	-.33*

*Notes. *, the correlation is significant at the .05 level (p-value ≤ .05, two-tailed); **, the correlation is significant at the .01 level (p-value ≤ .01, two-tailed). Only variables with significant correlations with other variables are presented in the table. Intensity of correlations: r < .4, low; 3 < r < 6, mild; r > 6, high.*

Figures

Figure 1. Flow chart illustrating patients' recruitment for all the evaluations.



5. Intervention

5.1 Article n. 4

Autogenic training for patients with organic diseases: a narrative review of the literature.

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Submitted.

Abstract

Objectives To examine the applications of autogenic training (AT) as a non–drug therapy to patients with organic diseases and their effects.

Methods In June 2021 PubMed, Ovid, Scopus, Embase, CINAHL, Web of Science, PsycINFO, and Cochrane Library were searched for original articles investigating the application of AT to patients with organic diseases. Thirty studies were found, and a narrative synthesis of their evidence was presented.

Results AT reduced psychological symptoms, pain, fatigue, and specific disease-related symptoms. AT favours a more functional adaptation to the disease, improving quality of life. It also has physiological effects, contributing to rebalancing the mind-body system. AT maintains its efficacy in the different forms it can be administered to patients.

Conclusion AT is a valid non-pharmacological option for patients with organic diseases. Further research is needed to bring reliable evidence to support even more the application of AT to medical conditions.

Keywords

Autogenic training, patients, organic disease, review.

Introduction

Autogenic Training (AT) is a non–drug technique and it is well known as one of the oldest biobehavioural techniques [Carruthers, 1979, Lehrer et al., 2007].

At the beginning of the 1920s, Dr. Johannes Heinrich Schultz, a German neurologist and psychiatrist, developed and promoted AT, which he considered a self–hypnotic procedure [Schultz & Luthe, 1959]. Wolfgang Luthe, one of Schultz's followers, described AT as an autonomic self–regulation therapy [Luthe, 1963].

AT is a standardized relaxation technique whose key aspects are six systematic formulas that refer to six different bodily functions: heaviness experience, the experience of warmth, regulation of the heart, regulation of breathing, regulation of visceral organs ("sun rays"), and regulation of the head.

The trainee must recite each formula silently with closed eyes six times and then he must repeat “I’m totally calm” once while laying down or sitting comfortably, and through progressive training, adding consecutively new formulas to the ones yet learned. [Lehrer et al., 2007].

These exercises facilitate autonomic self–regulation [Lehrer et al., 2007]. One of the most important aspects of AT is passive concentration, through which the patient tries to draw attention to his feelings instead of environmental stimuli. [Ramirez – Garcia et al., 2020].

AT is used to balance sympathetic tone and parasympathetic tone, allowing the shifting from the former to the latter, resulting in relaxation that extends toward all body systems which have been targeted by the formulas [Ramirez – Garcia et al., 2020].

AT can be used alone or in combination with other self–regulation methods, such as Progressive Muscle Relaxation (PMR), hypnosis [Lehrer et al., 2007], and biofeedback [Sadigh, 2001].

AT has been evidenced as an effective integrative treatment in various medical diseases, such as diabetes, HIV, and cancer [Kostić & Secen, 2000, Ramirez – Garcia et al., 2019, Minowa & Koitabashi, 2013]. More specifically, AT induces muscle and mental relaxation, which can lead to a reduction in stress and anxiety levels in chronic diseases that can be characterized by a long-term stress reaction, such as asthma, hypertension, tension-type headache, and psychosomatic disorders [Seo & Soukyoung, 2019, Seo et al., 2018, Kanji & Ernst, 2000].

This narrative review aims to summarize the applications of AT to patients with organic diseases and their effects.

Methods

The search for articles was conducted in June 2021 in the following databases: PubMed, Ovid, Scopus, Embase, CINAHL, Web of Science, PsycINFO, and Cochrane Library. Keywords included (MeSH and free words): Autogenic training [Mesh]; Autogenic training [Freetext]; Self-hypnosis [Freetext]; Autohypnosis [Thesaurus just in PsycINFO]. Then, a search update followed in August 2022 on the same databases.

Research studies investigating the application of AT to patients with organic diseases and its effect were included with no limitations related to publication date. Thirty studies were found, and a narrative synthesis of their evidence was presented.

Results

Methodological aspects

Country

Seven studies were conducted in the UK [Hidderley & Holt, 2004, Kanji et al., 2004, Kneebone et al., 2014, Golding et al., 2016, Golding et al., 2017, Golding et al., 2018, Kermani, 1987] 4 in Germany [Foerster, 1984, Bühl et al., 2019, Göhr et al., 1997, Bernateck et al., 2008], 4 in Japan [Minowa & Koitabashi, 2013, Minowa & Koitabashi, 2014, Fukunishi et al., 1997, Shinozaki et al., 2010], 2 in Russia [Aĭvazian et al., 1984, Aĭvazian et al., 1988], 2 in Poland [Szczepańska-Gieracha et al., 2021, Rutkowski et al., 2021], 1 in Italy [Rossi et al., 1989], 1 in Ireland [Wright et al., 2002], 1 in Spain [Álvarez-Melcón et al., 2018], 1 in Hungary [Zsombok et al., 2003], 1 in USA [Jones et al., 2014], 1 in Canada [Ramirez – Garcia et al., 2020],

1 in Australia [Sutherland et al., 2005], 1 in India [Ajimsha et al., 2014], 1 in Switzerland [Keel et al., 1998], 1 in Croatia [Kostić & Secen, 2000], 1 in Canary Island [Henry et al., 1993].

Objectives

Five studies evaluated the effect of AT on physiological parameters, such as immune system responses, cortisol levels, and blood values (i.e., HbA1c); 4 examined whether AT lowers anxiety levels; 1 considered the potential of AT to treat depression; 1 explored the effectiveness of AT in reducing self – reported tension; 1 evaluated the effects of AT on drug consumption; 3 investigated the antihypertensive efficacy of AT and 1 surveyed the possibility of AT application in a group of chronic asthmatic patients. One study examined the effectiveness of AT in students with a diagnosis of Tension-type headache. One study investigated the effects of AT on motor performance in Parkinson's Disease. Two studies compared the efficacy of AT with routine treatment. Five studies examined the combination of AT with other therapies. Five studies assessed the influence of AT on psychosocial aspects, well-being, and quality of life.

Samples

In most of the screened studies, participants aged between 35 and 93 years [Wright et al., 2002, Kneebone et al., 2014, Rutkowski et al., 2021, Minowa & Koitabashi, 2013, Minowa & Koitabashi, 2014]. There were also samples with a wider age range, with individuals aged 16-64 years [Foerster, 1984, Zsombok et al., 2003, Hidderley & Holt, 2004].

Finally, some studies have been carried out on very young subjects, e.g., children, young adolescents (9-14 years), and young adults (9- 25 years) [Göhr et al., 1997, Bühl et al., 2019, Álvarez-Melcón et al., 2018].

Sample sizes were various, from case reports [Bühl et al., 2019] to research with over 100 participants [Álvarez-Melcón et al., 2018].

The average sample size of the examined studies was 44 individuals.

Participants of the studies were affected by various organic diseases: oncological diseases, cardiovascular diseases, pulmonary diseases, headaches, AIDS, diabetes, neurodegenerative disorders, rheumatoid arthritis, and psychosomatic disorders.

AT applications

Few studies followed the principle of self-hypnosis proposed by J.H. Schultz and let participants try the exercises independently, without any help, after a brief description of the technique and a basic example. For example, in the study of Wright and colleagues [Wright et al., 2002], each patient diagnosed with cancer was given a brief explanation of how AT works, and, subsequently, it was requested to be applied three times a day for 10 weeks.

Other research opted for the inclusion of an instructor who could provide training information to individuals and control the exercises carried out by participants in his presence, evaluating any side effects or incorrect practice of AT. For instance, patients with acute leukemia were offered the opportunity to regularly perform the AT exercises together with an expert in this relaxation technique [Foerster, 1984]. Similarly, the research carried out by Henry and colleagues [1993] added weekly basis AT sessions with a therapist to the daily individual training practice.

Other investigations carried out what Schultz called “hetero – hypnosis”, that is hypnosis induced by a therapist [Lehrer et al., 2007]. In the studies conducted by Minowa and Koitabashi [Minowa & Koitabashi, 2013; Minowa & Koitabashi, 2014], the experimental group received a CD containing guided AT exercises. In the 2013 research [Minowa & Koitabashi, 2013] the same/ a similar CD was played by patients while they were subjected to an electrocardiogram, to be able to record any changes at the cardiovascular level during the practice of this relaxation technique. In the 2014 study [Minowa & Koitabashi, 2014] a CD was delivered to women diagnosed with breast cancer, pending surgery, and they were asked to practice AT three times a day for seven days after surgery. Even Golding and colleagues [Golding et al., 2016] offered the experimental subjects a CD containing instructions to carry out AT independently in their homes, indeed after a few months, they were allowed to decide whether to continue with the use of the CD and therefore AT.

Finally, in a 2008 study, participants were required to practice AT in small groups in the clinic and to practice daily in their homes with the help of an audio cassette [Bernateck et al., 2008].

AT was presented as a practice to perform individually, e.g., daily at home [Shinozaki et al., 2010, Foerster, 1984, Álvarez-Melcón et al., 2018] or to experience in small groups of 4-8 individuals [Kanji et al., 2004, Bernateck et al., 2008]. In the study conducted by Shinozaki [Shinozaki et al., 2010] there was an individual AT session for 8 weeks, combined with daily practice at home.

Outcomes assessment

The outcomes used as parameters of the effectiveness of AT can be distinguished into two main categories: those resulting from the use of psychological scales and those obtained from physiological and medical tests.

Regarding the first category, the most frequently used psychological tool was the Hospital Anxiety and Depression Scale (HADS) [Zigmond & Snaith, 1983, Golding et al., 2016, Rutkowski et al., 2021], assessing anxious and depressive symptoms.

Another tool used to detect state and trait anxiety was the State-Trait Anxiety Inventory (STAI) [Minowa & Koitabashi, 2013, Minowa & Koitabashi, 2014, Spielberger et al., 1983].

The Profile of Mood States (POMS) to evaluate mood was administered to people with multiple sclerosis in the pilot project conducted in Australia by Sutherland and colleagues [Sutherland et al., 2005].

A commonly used scale to assess pain was the Visual Analogue Scale [Scott e Huskisson, 1976]. This tool was also associated with the STAI to be able to evaluate both anxiety and pain, which are often interrelated [Minowa & Koitabashi, 2013; Bernateck et al., 2008].

Regarding the evaluation of stress, one study with subjects diagnosed with chronic obstructive pulmonary disease [Rutkowski et al., 2021] administered the Perception of Stress Questionnaire (PSQ) [Plopa & Makarowski, 2010].

Other diagnostic tools used by researchers are the 16 Personality Factors Questionnaire Form [Cattel et al., 1957] and the Middlesex Hospital Questionnaire (MHQ) [Crown & Crisp, 1970] to detect parameters such as phobic anxiety or obsessiveness [Rossi et al., 1989].

Other questionnaires were used in individual studies, often specific to the pathology examined, such as the Tension Rating Circles (Trcs), an adaptation of the Depression Intensity Scale Circles [Turner-Stokes et al., 2005]. The six vertically arranged circles represent the muscular tension experienced by the subject: the lower circle, without any shadow, corresponds to the absence of tension, while as you climb you proceed with a greater experience of muscular tension [Kneebone et al., 2014].

The Unified Parkinson's Disease Rating Scale (UPDRS) [Fahn & Elton, 1987], a standardized scale to quantify the signs and symptoms of Parkinson's disease and be able to assess their progress, was used to evaluate any improvements deriving from the daily practice of AT [Ajimsha et al., 2014].

As regards the evaluation of the effects of AT in patients with Irritable Bowel Syndrome (IBS), the results of several questionnaires were analyzed [Shinozaki et al., 2010]: the Self-reported Irritable Bowel Syndrome Questionnaire (SIBSQ) [Endo et al., 2000], related to several symptoms experienced by these subjects, such as bloating and abdominal pain; the Self — Rating Depression Scale (SDS) [Zung, 1965] and the Medical Outcome Short Form 36 Health Survey (SF-36) [Ware & Sherbourne, 1992], which analyses the quality of life.

In a study [Sutherland et al., 2005] patients with multiple sclerosis were asked to complete several scales which could provide information on the quality of life concerning the state of health, depressive symptoms, and social well-being after the AT sessions. The tests were respectively: the Multiple Sclerosis Quality of Life Instrument (MSQQL) [Vickrey et al., 1995], the Centre for Epidemiological Studies Depression Scale (CES — D) [Radloff, 1977], and the Multidimensional Scale of Perceived Social Support (MSPSS) [Zimet et al., 1990].

Concerning the second category of parameters, it ranges from values related to cardiovascular functioning, such as heart rate and high-frequency component,

detectable by an electrocardiogram [Minowa & Koitabashi, 2013], or blood pressure, in its diastolic and systolic components [Aĭvazian et al., 1988], to those related to the respiratory apparatus, including the forced vital capacity, the forced expiratory volume in the first second, forced expiratory flow between 25% and 75% of the forced vital capacity and mesoexpiratory flow [Henry et al., 1993] or the 6 min walk test [Singh et al., 2014] administered in Rutkowski's recent research [Rutkowski et al., 2021]. In addition, values regarding the immune system, such as the number of T and B lymphocytes in the body, CD8 (protein present on T9 lymphocytes and natural killer cells), immunoglobulin A (IgA), and cortisol production [Hidderley & Holt, 2004, Minowa & Koitabashi, 2014, Jones et al., 2014]. In the case of patients with diabetes, more specific values obtained through a simple blood sample were also considered, in particular blood sugar, blood glucose level (Hba1c or Ghb) [Göhr et al., 1997], lipids and lipid peroxidation [Kostić & Secen, 2000].

Results

1. Oncological diseases

AT provides both psychological and physical benefits to cancer patients.

Anxiety and depression appear to be the variables on which AT is most effective. It was found that, after an AT course lasting 10 weeks, there was a significant reduction in anxiety and an increase in coping "fighting spirit" compared to the pre-training period [Wright et al., 2002].

Another study reported that in patients practicing AT in the days immediately following the mastectomy levels of anxiety and pain were significantly lower than in the control group [Minowa & Koitabashi, 2013]. A greater sense of relaxation was

achieved following the constant practice of AT in two other studies on patients with leukemia [Foerster, 1984, Bühl et al., 2019].

Other studies examined various immune system indices and they found a positive impact of AT on the immune response [Hidderley & Holt, 2004, Minowa & Koitabashi, 2014]. Indeed, AT had improved the levels of CD8 (a T cell protein) and natural killer cells, involved in the recognition and elimination of cancer cells [Hidderley & Holt, 2004]. It was finally found that AT was responsible for a significant increase in sIgA (salivary immunoglobulin A) after 7 days from surgery [Minowa & Koitabashi, 2014].

2. Cardiovascular diseases

Several studies applied the AT technique in patients with cardiovascular diseases and they concluded that it favours the lowering of blood pressure in both its systolic and diastolic components [Herrmann, 2002, Kanji et al., 1999]. Various research found that AT had an antihypertensive effect and improved the hemodynamic parameters [Aĭvazian et al., 1984, Aĭvazian et al., 1988]. Rossi and colleagues [Rossi et al., 1989] found that AT had both physiological and psychological beneficial effects. Regarding the former, patients who continued to practice AT even after 8 months had lower diastolic blood pressure values than the control group, while no differences in heart rate were detected. Regarding the latter, in patients practicing AT there was a significant decrease in fluctuating anxiety, obsessiveness, and somatic disorders.

Another study on patients with coronary artery disease showed a significant difference in anxiety between patients practicing AT and the control group, and this result seemed to persist even in the follow-up five months after treatment [Kanji et al., 2004].

Finally, AT determined a significant reduction in tension and anxiety in post-stroke patients with the maintenance of these results during the first months of follow-up [Kneebone et al., 2014, Golding et al., 2016, Golding et al., 2017, Golding et al., 2018].

3. Pulmonary diseases

AT seemed to be an adequate additional therapy to the treatment of bronchial asthma, considering its effect of reduction of anxiety and shifting from the activation of the sympathetic system to that of the parasympathetic one [Schaeffer & Freytag — Klinger, 1975]. Research conducted by Henry and colleagues [Henry et al., 1993] found that, together with appropriate drug therapy, AT resulted in significant improvements in some examined physiological parameters: Forced Vital Capacity (FVC) and Forced Expiratory Volume in the first second (FEV1). Other improvements, although less significant, have been reported regarding the Forced Expiratory Flow and the Meso-expiratory Flow. Thus, AT brought a great benefit, leading to a reduction of obstruction at the airway level [Erskine – Milliss & Schonell, 1981].

Unfortunately, however, some reviews have highlighted that AT does not have a significant beneficial effect on asthma patients [Huntley et al., 2002, Györik & Brutsche, 2004].

Finally, a recent study on patients suffering from Chronic Obstructive Pulmonary Disease evidenced that AT contributes to the improvement of lung function and the ability to perform physical exercise [Rutkowski et al., 2021].

4. Headache

A review conducted by Kanji and collaborators [Kanji et al., 2006] examined the role of AT in treating headaches. What has come to light is that given the low number of clinical trials checked, there is insufficient evidence that AT may be more effective than other interventions, such as hypnosis or biofeedback.

Later studies have reversed, at least in part, that result. A Spanish study on students who had been diagnosed with tension-type headaches evidenced a decrease in the frequency of headaches after 4 weeks of AT and during follow-up with a potentiated effect when kinesiotherapy and posture correction training were integrated with AT [Álvarez-Melcón et al., 2018]. AT reduced also the duration of headache, the pain intensity, and the use of analgesics.

A study conducted in Hungary on women with mixed headaches, migraine, and tension-type headaches showed that after AT, there was a decrease in both the frequency of headaches and the intake of analgesics, antimigraine, and anxiolytics in all subgroups [Zsombok et al., 2003].

Also, another 2012 study highlighted how the combination of traditional drug treatment and AT results in an improvement in the scores of headaches and a reduction in the consumption of analgesics [Pickering et al., 2012].

5. AIDS

A 2019 review [Ramirez – Garcia et al., 2019] highlighted the effects of TA on patients with AIDS as reported by a trial [Kermani, 1987]. The principal result was a higher quality of life and a stable improvement in those patients who perform AT for more than four months on a regular daily basis. Moreover, thanks to AT, patients could better manage the most disabling and unwanted symptoms, such as pain,

diarrhea, night sweat, and weight loss. Finally, AT seemed to have a positive impact on the average life expectancy of people with AIDS (18.5 months versus 13.5).

Another recent study evidenced that 71% of HIV patients practicing AT completed all the established sessions and found numerous positive effects, including better management of emotions and an improvement in both quality of life and depressive symptoms [Ramirez – Garcia et al., 2020]. Furthermore, in a study analyzing a subgroup of patients with HIV in the early stages of the infection practicing AT, it has been observed a significant reduction of anxiety, fatigue, and confusion between pre- and post-AT treatment [Fukunishi et al., 1997].

At the same time, another study showed that AT seemed not to have a significant effect in the reduction of cortisol levels in patients with AIDS, for which, instead, progressive muscle relaxation, diaphragmatic respiration and guided imagination had a relevant role in the short-term [Jones et al., 2014].

6. Diabetes

A study from 1997 tested the psychological effects of AT delivered to children and young adolescents with type 1 diabetes [Göhr et al., 1997]: After AT treatment, there was a score reduction in emotional lability, the tendency to addiction to adults, the need for aggressive forms of dominant behavior and the feeling of submission to others. In addition, an increase in self-confidence regarding the ability to plan, make decisions and be aware of one's meaning in life was evidenced. Moreover, AT treatment determined fewer attention difficulties, aggressiveness, nervousness, and anxiety. Relatively to the physiological effects, no decrease in the HbA1 (hemoglobin subunit alpha 1) was detected.

A study conducted in 2000 highlighted how AT can be an alternative therapy for individuals with type 2 diabetes that can improve glucose control and lipid metabolism and reduce levels of HbA1, fasting blood sugar, and lipid peroxidation [Kostić. & Secen, 2000].

7. Neurodegenerative disorders

One Australian research investigated the psychological effects of AT in people with multiple sclerosis: it reported an improvement in quality of life, i.e., a reduction of pain, role limitations due to physical problems, role limitations due to emotional problems, and fatigue, and an enhancing of energy and vigor, but not significant variations in depression [Sutherland et al., 2005].

An Indian study on patients with Parkinson's disease studied AT in integration with physiotherapy and showed that AT contributed to the improvement of motor symptoms such as facial expression, rigidity, tremor, finger taps, hand movements, and rapid alternating movements also after 12 follow-up weeks [Ajimsha et al., 2014].

8. Rheumatoid arthritis

Bernateck and colleagues (2008) assessed the effect of AT in patients with rheumatoid arthritis and evidenced a reduction in pain intensity at the seventh week of treatment and its maintenance three months after the end of treatment. As compared with auricular electroacupuncture, AT effects were slower and less marked in the presentation, but effective. Moreover, patients reported a reduction in the consumption of regular analgesics and were satisfied with AT treatment [Bernateck et al., 2008].

9. Psychosomatic disorders

A study conducted in the 90s [Keel et al., 1998] on AT with patients with fibromyalgia showed reduced drug use and reduced use of physiotherapy, fewer sleep disorders, reduced pain, an improvement of general symptoms, and patient's perception of their health status.

A 2015 review highlighted how AT is effective in reducing fibromyalgia pain because it includes physical exercises, aware observation of the illness, acceptance, and relaxation. However, in the follow — up pain increased in the group who practiced only AT, while pain decreased in the group receiving integrated therapies. Thus, AT seems to be more effective when integrated with other interventions, such as psychoeducation [Meeus et al., 2015].

Finally, Shinozaki and colleagues (2010) studied AT for patients with irritable bowel syndrome and highlighted that the proportion of patients experiencing adequate relief from the disease-related abdominal pain or discomfort after the AT sessions was higher than that of patients of the control group: social functioning and bodily pain improved in the experimental group, while no statistically significant changes in emotional wellbeing and general health status were observed [Shinozaki et al., 2010].

Discussion

The collected evidence suggests that AT is an effective relaxation technique for patients with different medical diseases. It has multiple effects. It improves the quality of life, functioning, performances in daily life activities, and self-efficacy [Fukunishi et al., 1997]. It positively contributes to emotional regulation and the management of other symptoms, such as pain and fatigue [Sutherland et al., 2005].

AT can reduce anxiety and depression, favour functional coping, and can reduce the use of drugs [Wright et al., 2002; Foerster, 1984; Hidderley & Holt, 2004; Kanji et al., 2004; Zsombok et al., 2003]. Finally, AT has physiological effects, such as the improvement of the immune response [Hidderley & Holt, 2004; Minowa & Koitabashi, 2014] and the increase in parasympathetic activities [Aĭvazian et al., 1984; Aĭvazian et al., 1988; Rossi et al., 1989; Kanji et al., 2004]. Moreover, it can improve the peculiar symptoms of diverse diseases, e.g., blood pressure for cardiovascular diseases, or asthma and lung function in pulmonary diseases [Aĭvazian et al., 1984; Aĭvazian et al., 1988; Henry et al., 1993; Rutkowsky et al., 2021]. These effects have been observed also in the follow-up, so they seem to last even in the long term after the end of the treatment [Golding et al., 2016; Golding et al., 2017; Golding et al., 2018]. In this regard, the only exception was observed in patients with Parkinson's disease, because AT was effective only while actually being conducted, while it has no long-term effects once discontinued. It is possible that for complex clinical conditions AT must be continued to provide its effects [Ajimsha et al., 2014].

Finally, AT appears to be most effective when combined with other treatments, such as psychotherapy, pulmonary rehabilitation program, physical therapy, posture correction exercises, and progressive muscle relaxation [Foerster, 1984; Rutkowski et al., 2021; Álvarez-Melcón et al., 2018; Zsombok et al., 2003; Fukunishi et al., 1997; Ajimsha et al., 2014].

Although Schultz remarked on the importance of self-hypnosis and passive individual concentration during an AT session, the emerged results seem to be equally promising, both in case the subjects learn the technique by themselves, and when they are guided by an external subject during the exercises, such as an instructor.

AT seems to be effective in both individual and group treatment. If administered individually, it is more individualized and modifiable based on the needs of the patient and the outcome to achieve. At the same time, it requires to patients more economic resources. If taught to a group of patients, the treatment costs reduce, and more compliance could be obtained thanks to inter-individual cohesion. For these reasons, the rate of dropout, a phenomenon that characterized some studies [Aĭvazian et al., 1988; Herrmann, 2002; Rossi et al., 1989] can reduce. On the other hand, the focus on each participant is inevitably reduced [Hidderley & Holt, 2004].

Most of the analyzed studies had small samples, whereby a high degree of generalization of their results cannot be guaranteed. Moreover, the scarce number of studies specifically on AT, and their poor methodology, i.e. small samples, wide age range, and different applications of AT, could have negatively impacted data and their interpretation. And some evidence reported in some research was not confirmed by other studies or they are not sufficient. For example, research on AT for patients with other neurodegenerative diseases and psychosomatic conditions, i.e., nociplastic pain, or for patients with dermatologic diseases, gastrointestinal diseases, or in different oncological phases of illness, i.e., palliative care, are missing. In this regard, surprisingly, very limited amount of study on neurodegenerative diseases was performed. Studies on psychological interventions for these clinical populations are already scarce. And more importance may have been given to other types of psychological interventions, with the result that there is a significant study gap on AT in the neurodegenerative area. Thus, the implementation of further randomized trials on AT is stressed to draw far-reaching conclusions.

Conclusions

AT is a valid non-pharmacological option for patients with organic diseases, that can guarantee interesting positive effects, both of psychological and physiological type. It favours a more functional adaptation to the disease, improving symptoms and quality of life, and contributing to rebalancing the mind-body system. AT maintains its efficacy in the different forms it can be administered to patients.

Further research is needed to bring reliable evidence to support even more the application of AT to medical conditions.

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TABLES

Table 1. Characteristics of the included studies.

Oncological diseases		
Study		
Wright et al., 2002 Ireland	Objective Sample Intervention Outcomes Results	To increase coping ability in patients diagnosed with cancer 18 adults who were diagnosed with cancer, age: 40-80 years Individual AT three times a day at home Levels of anxiety and depression: HADS and POMS A statistically significant reduction in anxiety (HADS), an increase in "fighting spirit" (POMS), with an improved sense of coping and sleep being
Minowa & Koitabashi, 2013 Japan	Objective Sample Intervention Outcomes Results	To investigate the impact of AT on perioperative anxiety and pain in patients with breast cancer 60 women diagnosed with breast cancer, age: > 20 Individual AT with a CD three times a day within three days after surgery or control group Level of anxiety: STAI (Japanese version: STAI – JYZ); Level of pain: VAS;

		parasympathetic nervous system activity: HR, amplitude of HF component In the experimental group: significantly decreased anxiety score and pain score during postoperative three days; a significant increase in HF amplitude on all three days
Foerster, 1984 Germany	Objective Sample Intervention Outcomes Results	To investigate the efficacy of AT combined with psychotherapy 11 patients with acute leukosis in the isolation unit, age: 16 – 64 years Regular discussions with mutual AT Missing Increased relaxation and sense of agency
Bühl et al., 2019 Germany	Objective Sample Intervention Outcomes Results	To evaluate the feasibility and safety of an exercise intervention A 22 years – old man with DS who was undergoing high – dose chemotherapy for acute lymphoblastic leukemia An exercise program 3 times per week over a 5 — week period, targeting 30 minutes per session. AT training modified for people with cognitive impairments lasted 15 – 30 minutes Physical capacity; fatigue; adherence rate

		Adherence rate: 100%; AT might have determined a moderate sense of relaxation and pain relief
Hidderley & Holt, 2004 UK	Objective Sample Intervention Outcomes Results	To describe how AT was used on a group of early-stage cancer and the observed effect on stress – related behaviours and immune system responses 31 early – stage breast cancer women, having received a lumpectomy and adjuvant radiotherapy, age: 16 – 65 years Missing Level of anxiety and depression: HADS; immune system responses: T and B cell markers; observation of AT patients for evidence of a meditative state In the experimental group: a statistical improvement in HADS score; those women observed in a meditative state were found to have an increase in their immune responses
Minowa & Koitabashi, 2014 Japan	Objective Sample Intervention Outcomes	To investigate the effect of AT on sIgA in breast cancer surgery patients Women scheduled for breast cancer surgery, age: > 20 Individual AT with a CD three times a day within seven days after surgery or control group

	Results	Trait anxiety score: STAI (Japanese version: STAY – JYZ); sIgA: collection of salivary samples; HRV In the experimental group: significantly higher levels of sIgA on the 7th day after surgery
Cardiovascular diseases		
Aĭvazian et al., 1984 Russia	Objective Sample Intervention Outcomes Results	To compare the efficacy of AT with routine hypertension treatment 110 patients with hypertension Missing Psychological status; anti-hypertensive effect; hemodynamic parameters With AT there are: a higher anti – hypertensive effect, better hemodynamic parameters and an improvement in the psychological status of patients
Aĭvazian et al., 1988 Russia	Objective Sample Intervention Outcomes Results	To investigate the efficacy of AT in patients with hypertension 117 patients with labile essential hypertension Missing Physiological parameters: diastolic and systolic arterial BP, total peripheral resistance; Psychological parameters; hypertensive response to emotional stress, psychological

		adaptation, quality of life and working capacity With AT there are improvements both in physiological and psychological parameters. There is a positive correlation between AT efficacy and BP levels prior to treatment. There is also a negative correlation between AT efficacy and the duration of the disease
Rossi et al., 1989 Italy	Objective Sample Intervention Outcomes Results	To evaluate the anti – hypertensive efficacy of AT in a group of untreated patients with mild essential hypertension 10 previously untreated patients with mild essential hypertension, age: 18 – 50 AT three times a day at fixed times for ten weeks, combined with a placebo Physiological parameters: BP, HR; Psychological parameters: 16 – PF and MHQ to evaluate clinical abnormalities, MPI to measure neuroticism and extroversion Placebo: a non-significant decrease for BP AT: during the 3rd month systolic BP was significantly reduced, while at the 5th month diastolic BP was significantly reduced; a significant decrease in free –

		floating anxiety, in obsessivity, and in somatic complaints (subscales of MHQ)
Kanji et al., 2004 UK	Objective Sample Intervention Outcomes Results	To examine whether AT lowers anxiety levels experienced by patients undergoing coronary angioplasty 59 patients with CAD waiting for coronary angioplasty AT in small groups (8 patients) and individually every day + standard care for 5 months or control group Level of anxiety: STAI; BP and HR; QLI; subjective experiences recorded in a diary In the experimental group: a significant decrease of the level of anxiety both at 2 and 5 months; a decrease of diastolic BP; subjective experience of relaxation, improved wellness, and empowerment
Szczepańska-Gieracha et al., 2021 Poland	Objective Sample Intervention Outcomes Results	To compare the effect of VR therapy on the mental state of patients with CAD with AT 34 patients with CAD and elevated anxiety or depression symptoms VR + CR (experimental group) or AT + CR (control group) two times a week for four weeks Levels of anxiety and depression: HADS; PSQ

		In the experimental group: a significant decrease in HADS score (both anxiety and depression) and in PSQ In the control group: HADS and PSQ data did not change
Kneebone et al., 2014 UK	Objective Sample Intervention Outcomes Results	To consider the feasibility of setting up a relaxation group to treat symptoms of post stroke anxiety in an in – patient post – acute setting and to explore the effectiveness of relaxation training in reducing self – reported tension 55 stroke patients, age: 35 – 93 years AT in group weekly Measure of tension reduction: TRCs A significant reduction in self – reported tension following AT
Golding et al., 2016 UK	Objective Sample Intervention Outcomes Results	To consider relaxation as a potential treatment for anxiety in stroke survivors living in the community, including feasibility and acceptability 21 stroke survivors who reported experiencing anxiety (HADS – A $\geq$ 6) AT with a CD five times weekly for at least one month or control group HADS

		Participants who received AT were significantly more likely to report reduced anxiety compared to the control group
Golding et al., 2017 UK	Objective Sample Intervention Outcomes Results	To follow up participants in a randomised controlled trial of AT for anxiety after stroke at 12 months 15 of 21 original participants with post – stroke anxiety AT with a CD five time a week for a month, immediately in the intervention group and after three months in the control group HADS – A Anxiety ratings reduced significantly between pre and post – intervention and between pre – intervention and one year follow – up. The reduction from post – intervention to one year follow – up did not reach significance following correction
Golding et al., 2018 UK	Objective Sample Intervention Outcomes Results	To consider the potential of self – help relaxation training to treat depression after stroke 21 people with stroke, aged 49-82 years AT with a CD five times weekly for one month or control group HADS – D

		No difference between the experimental and the control group in depression scores. On two follow ups, however, significant positive differences were found for the experimental group
Pulmonary diseases		
Henry et al., 1993 Canary Islands	Objective Sample Intervention Outcomes Results	To evaluate the possibility of AT application in a group of chronic asthmatic patients 24 patients with chronic asthma, age: 18 – 60 years Individual AT three times daily for eight months or control group FVC, FEV1, FEF 25 – 75%, MEF 50% In the experimental group: high significant improvement in the respiratory function, particularly in FVC and FEV1
Rutkowski et al., 2021 Poland	Objective Sample Intervention	To determine whether the implementation of immersive reality during a pulmonary rehabilitation program would produce a more efficiency in reduction in symptoms of depression and anxiety, as well as stress level in patients with COPD 50 patients diagnosed as having COPD, age: 45 – 85 years, an HADS score > 8 VR + pulmonary rehabilitation programme or AT + pulmonary rehabilitation

	Outcomes Results	programme five times a week for two weeks PSQ and HADS as primary outcome; physiological parameters: 6 min walk test, lung function Both groups showed efficacy, however the one with VR seems more efficient in all the parameters examined
Headache		
Álvarez-Melcón et al., 2018 Spain	Objective Sample Intervention Outcomes Results	To evaluate the effectiveness of physical therapy based on cervical spine kinesiotherapy and posture correction exercises compared to a programme of AT 152 university students with a diagnosis of Tension – type headache, age: 18 – 25 years AT or AT + the other interventions once daily for four weeks Frequency, intensity, and duration of pain; drug consumption Both interventions achieved a decrease in all the parameters of pain; however, decreases in frequency and intensity were more significant in the combined treatment group. A decrease in analgesic consumption was also achieved in the combined treatment group

Zsombok et al., 2003 Hungary	Objective Sample Intervention Outcomes Results	To examine the effects of AT on headache – related drug consumption and headache frequency in patients with migraine, tension – type, or mixed (migraine plus tension – type) headache over an 8 – month period 25 women, aged 16 – 55 years, with primary headache: 11 with mixed headache, 8 with migraine, and 6 with tension – type headache Individual AT on a daily basis + once a week with a therapist for four months. AT was supplemented with cognitive therapy to identify and modify maladaptive cognitive coping responses Headache frequencies; consumption of drugs (antimigraines, anxiolytics, analgesics) The treatment significantly reduced frequently of headaches and use of anxiolytic, antimigraine and analgesic drugs in all subgroups. AT was most effective in tension – type headache
AIDS		
Kermani, 1987 UK	Objective	To evaluate the efficacy of AT on patients with AIDS and to see if it would influence the course of the disease in any way

	Sample Intervention Outcomes Results	14 patients suffering from AIDS, 14 asymptomatic carriers, 6 with PGL, and 6 with ARC Group AT for seven weeks PSE and QL The quality of life significantly and consistently improves, no matter what their diagnosis was. This improvement seems to be maintained by those who have been doing it for longer than four months at least once a day. AT seems to influence the average survival: 18,5 months is greater than 13,5 months
Jones et al., 2014 USA	Objective Sample Intervention Outcomes Results	To determine the effects of relaxation techniques on cortisol levels in HIV – seropositive women 150 HIV — seropositive women CBSM + relaxation techniques (PMR, guided imagery with diaphragmatic breathing, AT) for ten weekly sessions Salivary cortisol collected during session 1,4,7 and 10 of the intervention Guided imagery with diaphragmatic breathing was the most effective in cortisol reduction in the group intervention condition. PMR was the most effective strategy in the individual condition. AT,

		instead, doesn't seem to be effective in cortisol reduction
Ramirez – Garcia et al., 2020 Canada	Objective Sample Intervention Outcomes Results	To assess the feasibility and acceptability of PMR and AT interventions among people living with HIV who have depressive symptoms 54 patients with HIV AT or PMR interventions consisted of 6 six session of individual training over twelve weeks, plus home practice Missing Participants reported better emotion management and improvements in depressive symptoms and quality of life
Fukunishi et al., 1997 Japan	Objective Sample Intervention Outcomes Results	To examine the efficacy of relaxation techniques in a sample of HIV patients without AIDS in the early stages after infection 19 HIV positive patents without AIDS AT + PMR or ordinary supportive psychotherapy or no psychiatric treatment POMS After relaxation score for anxiety, fatigue, depression and confusion were significantly lower. However, relaxation techniques seem to be ineffective as for the reduction of anger

Diabetes		
Göhr et al., 1997 Germany	Objective Sample Intervention Outcomes Results	To discuss psychosocial influences of diabetes mellitus type 1 on children and young patients 21 patients with diabetes mellitus type 1, age: 9 – 14 years Individual AT for eleven weeks PFK 9 – 14 (psychological parameter) and HbA1c (physiological parameter) Significant reduction in some PFK subscale: "need for aggressive forms of dominance behaviour", "feeling of submission with respects to other", "emotional lability", "tendency for dependence on adults" and "neuroticism". Significantly increased score in the PFK subscale "self-confidence regarding one's own meaning, decision and planning". There was no reduction in HbA1 scores.
Kostić & Secen, 2000 Croatia	Objective Sample Intervention Outcomes Results	To examine the benefits of AT in patients with type 2 diabetes 40 patients with type 2 diabetes AT for twelve weeks HbA1c levels, glycemia, lipids and lipid peroxidase Decreased levels of HbA1c, fasting glucose and lipid peroxidase

Neurodegenerative disorders		
Sutherland et al., 2005 Australia	Objective Sample Intervention Outcomes Results	To explore the effect of an AT program on the HRQOL and well – being for people with MS 22 people with confirmed diagnoses of MS One AT supervised training session per week for ten weeks and individual AT once a day or control group MSQOL (for HRQOL); POMS – SF (for mood states); CES – D (for depression); MSPSS (for social support) There were some improvements in aspects of HRQOL as measured by the MSQOL (pain, role limitations due to emotional problems) for the AT group in comparison to the control group. The improvement in the energy subscale of MSQOL is linked to an improvement in fatigue and vigor subscales of POMS – SF. Depressed affect, measured by CES – D, showed a large effect, however, it is not statistically significant.
Ajimsha et al., 2014 India	Objective Sample Intervention	To investigate whether AT when used as an adjunct to PT improves motor performances in PD in comparison with a control group receiving PT alone 66 patients with PD

	Outcomes Results	AT group or control group, 40 session per patient over eight weeks Motor subscale of UPDRS (to measure the motor performances) There were significant main effects of time, group, and the time x group interaction, thus the AT, when used as an adjunct to PT, is more effective than PT alone in improving motor performances in PD patients. However, the follow – up at week 12 has shown that the treatment effects were less evident compared with week 8 after the treatment: AT is only effective while is actually being conducted, it doesn't have long – lasting effects once discontinued
Rheumatoid arthritis		
Bernateck et al., 2008 Germany	Objective Sample Intervention	To compare the efficacy of EA with AT in rheumatoid arthritis 37 patients with rheumatoid arthritis, age: 18 – 67 years, suffering from rheumatoid arthritis ≥ 6 months, average pain intensity of ≥ 3 (VAS) in the 7 days before the baseline assessment despite pharmacological analgesia and/or disease modifying antirheumatic drugs

	Outcomes	EA once a week for 48 hours at home for six weeks or group AT (4-6 people) once a week for six weeks + individual AT every day
	Results	VAS and PDI (for the pain intensity); DAS 28 (for the disease activity); CGI (for clinical global impression); ESR and pro inflammatory cytokine levels In both groups there is a meaningful and statistically significant improvement in all outcome parameters. In the EA group significant reduction in the VAS values could be already observed after the 2nd treatment week, while in the AT group that could be observed only after the 6th week. Patients from both groups considered their treatment successful, however patients in the EA group assessed their outcome to be significantly more markedly improved than patients in the AT group. In the AT group there is no change in ESR and cytokine levels, while in the EA group the ESR was significantly reduced after 3 treatments, but not at the end of the treatment.

		In both groups a significant reduction in the consumption of regular analgesics was observed
Psychosomatic disorders		
Keel et al., 1998 Switzerland	Objective Sample Intervention Outcomes Results	To test the efficacy of an integrated, psychological treatment program in a controlled study involving patients with fibromyalgia 27 patients with fibromyalgia 15 weekly group sessions of the integrated psychological treatment program (information, instruction in self – control strategies, gymnastics, relaxation, and group discussion) or control group A semi structured psychiatric interview; FPI; Locus of Control Scale; Rosenzweig Picture Frustration Test (German version) In the experimental group: improvement of at least 50% or a positive patient rating occurred in the following parameters: medication consumption, physical therapies, sleep disturbances, pain score, patients' global assessment, general symptoms.
Shinozaki et al., 2010 Japan	Objective Sample	To test the hypothesis that AT improves symptoms of IBS 21 patients with IBS

	Intervention Outcomes Results	Individual AT for eight sessions in eight weeks or control group (discussing diet therapy) Adequate relief to assess improvement of abdominal pain and/or discomfort: "Did you have adequate relief of IBS – related abdominal pain or discomfort?" (The answer was either "Yes" or "No"); SIBQ; STAI; SDS; SF -36 The proportion of adequate relief in the last AT session in the AT group was significantly higher than that in the controls. Two subscales of the SF – 36 ("social functioning and bodily pain) were significantly improved in the AT group. Role emotional and general health showed a tendency for improvement in the AT group

5.2 Article n. 5

Cognitive-constructivist psychotherapy for patients with multiple sclerosis: a case report.

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Submitted.

Abstract

Multiple sclerosis (MS) is a chronic neurodegenerative disease with no resolutive medical treatments eliciting various symptoms. Thus, the impact of MS on the individual can be significant, and MS patients can suffer from reduced quality of life, difficulties in adaptation to the disease, and psychological distress.

Psychotherapy favors the patient's functional adaptation to MS. Cognitive-constructivist psychotherapy intends the individual as a self-system that attributes subjective meanings and reacts in a subjective way to the events it lives. It helps the

patient in reorganizing his immediate and implicit experience into more understandable and manageable explicit maps.

Through this case report, a brief intervention of cognitive-constructivist psychotherapy with a patient with RR-MS is presented.

The intervention seemed to be effective because it favored more functional coping strategies and patients' symptoms became less intense and more masterable. In the face of inescapable disease, moving the attentive focus from the disease to the patient opens numerous possibilities to increase his quality of life regardless of how the disease goes. In this sense, psychotherapy represents a lifetime personal opportunity of observation and change and a psychological intervention that, when necessary, should more and more be integrated with others, from a bio-psycho-social perspective of patients' care.

Keywords

Multiple sclerosis, psychotherapy, constructivism, psychological intervention, distress

Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disease that is characterized by sclerotization [1]. Relapsing-remitting MS (RR-MS) is the most common MS subtype. Its progression consists of the alternation of episodes of worsening and periods of recovery or stability [2]. MS patients are typically affected by sensory and motor disorders, fatigue, pain, cognitive impairment, and other body dysfunctions [3]. Nevertheless, the presence and intensity of symptoms vary from patient to

patient. MS is considered a neurodegenerative disease because, although it can be well controlled with medical therapies and its course can be slow, there are no resolutive treatments that stop its progression. For these reasons, the impact of MS on the individual can be significant, and MS patients can suffer from reduced quality of life, difficulties in adaptation to the disease, and psychological distress [3, 4].

When appropriate and necessary, psychotherapy favors the patient's functional adaptation to the disease. Psychotherapy helps the patient to regulate his emotional, cognitive, and behavioral reactions to the disease-related stimuli that solicit his "mind-body system" and to integrate the perturbations that the disease exerts on his balance [5]. Data from randomized trials and neuroimaging confirm the positive effects of psychotherapy in MS patients [6]. The psychotherapeutic intervention increases MS patients' quality of life and reduces symptoms such as anxiety, depression, and fatigue [7].

Cognitive-constructivist psychotherapy intends the individual as a self-system that attributes subjective meanings and reacts in a subjective emotional, cognitive, bodily, and behavioral way to the events or situations it lives [8]. These meanings and reactions are due to the internal functioning of the system, created and maintained across the individual's life story [9]. Psychotherapy acts in the direction of reorganizing a patient's immediate and implicit experience into more understandable and manageable explicit maps [8]. It has the aim to favor the patient's awareness of his meanings, reactions, and internal functioning, with the hypothesis that better knowledge means better management and the possibility of changes towards more functional ways of giving meaning to events and responding to them [10].

In the following paragraphs, a brief intervention of cognitive-constructivist psychotherapy with a patient with RR-MS is presented.

Case presentation

At the beginning of the intervention, V. was 62 years old. She was affected by RR-MS. She received the MS diagnosis in February 2020, and she subsequently started the medical therapies. Her MS was stable and slow in its progression. Her main disease-related physical symptom was fatigue, but this symptom did not have a heavy impact on her quality of life.

V. was married and had a daughter and a young grandson. V. was retired.

In March 2021 V. came of her choice at the Clinical Psychology Unit of "Città della Salute e della Scienza" Hospital because of anxious symptoms and difficulties in adaptation to the disease. She met the criteria for the anxiety disorder [11]. She lived the diagnostic communication as "a shock", feeling fear and worries for the future, uncertainty about the disease progression, and loss of control. She reported insomnia, early awakening, anxiety, agitation, and depressive symptoms. She tried to distract her mind, but her thoughts were focused on disease and the future. She also reported trait anxiety as one of her identity characteristics. Her vital functions were preserved. She hoped to maintain her autonomy and freedom despite the disease: being able to do what she desires. Her principal worry about MS was ending up in a wheelchair and having to depend on everybody. In this regard, V. declared to have the intention to refer to an association for euthanasia as extreme action to control her life when she will lose her autonomy. At the same time, V. shared that she needed help in managing her present.

Methods

V. received eight meetings of individual cognitive-constructivist psychotherapy weekly. The number of meetings is established by the Unit direction due to spending

review, to guarantee to patients brief interventions of psychotherapy and psychological support that help them in facing their present-related difficulties in the adaptation to the medical disease.

Each meeting lasted an hour. Informed consent to the collection and publication of data was obtained from V.

The cognitive-constructivist psychotherapy adapted for eight sessions

During the first meetings the therapeutic alliance is built and throughout the entire intervention, attention is given to the therapist-patient relationship. It is being monitored and possible interpersonal dysfunctional cycles are intercepted and explicitly observed, to maintain a cooperative relationship between the therapist and the patient.

From the beginning, a kind, welcoming and non-judgmental attitude towards patients' contents is cultivated by both the therapist and the patients, also through mindfulness-based practices and techniques if it is necessary.

The psychotherapy was adapted for eight sessions as follows:

- 1 and 2 sessions: patient welcome; analysis of the patient's needs and demands; investigation of patients' medical history; exploration of symptoms and diagnostic framework; description of the intervention; definition of the therapeutic goals, contract, and setting; investigation of patient's personal and familiar history; symptoms history and reformulation; assumptions about attachment style and personal meaning organization styles [12]; identification of patients' critical themes, exploration of patients' limits and resources.

- 3-7 sessions: stimulation of patient's observation, formal regulation, and management of his thoughts, emotions, and bodily sensations; exploration of patient's cognitive, emotional, relational, and behavioral responses to increase patient's awareness of his internal and relational functioning and favor his search for more adaptive coping strategies; application of techniques such as the "slow motion" [13], assignment of homework and mindfulness-based strategies [14].

- 8 session: shared observation of the whole path; mentalization on the effects of the therapy, the acquired awareness, the symptoms state and the possible occurred changes; analysis of possible critical issues still present and evaluation of future directions.

The intervention

Sessions 1 and 2

The information reported in the "Case presentation" section was collected.

V. focused on the symptoms that affected her in her present: the feeling of having lost force, not having positive thoughts, not having desires, deflected mood, and the feeling that she cannot face her situation alone. She reacted to her condition with shock and anger, she tried to fight but resignation arrived. She felt to have lost her battle against life because she realized that she could not modify its course. She was trying to exert control of MS, but she realized she was failing. V. felt anxiety and worries related to the feeling of not having control over MS: she said, "I hope to be able to take care of myself till the end of life, but I am uncertainty about it".

At the same time, she added that, in general, when she gave up stopping to search for control, she felt better: she felt less tension, peace, calm, and security. She

described this state as a private neutral and light zone that was very protective for her. V. used this zone to block rumination and obtain energy.

In this regard, she realized that when she thought that everything depended on her, she tended to activate, perform, fight, and control. On the contrary, when she realized that she could not control everything she stopped and found peace.

Thus, she focused on the desire to limit what she did, dedicating only to what she could do, also relative to MS.

About this, V. mentalized that concerning the MS she had not yet been able to reach this "zen point" because of her high fear of the future and disease progression, which enhanced her control level. Moreover, MS was determining a reduction of her physical and mental health, and it was perceived by V. as a strong threat. Moreover, V.'s control on MS was reduced and MS limited her possibilities. The final effect was a deflected mood. Moreover, V.'s attention was constantly focused on MS and a continuous alert state was activated towards her body and its signals.

V. recognized that this anxious condition was not useful for her: she would like to be less reactive towards her symptoms, to accept MS, and to better live together with it. At the same time, she realized that she was acting automatically, as she was not completely present in herself. She recognized that she was anxious, but she could not manage it.

Therefore, we started a work oriented to the acquisition of symptom awareness, the emotions validation, and the symptoms rereading in light of V.'s functioning. Furthermore, we shared that shifting the attention and control from MS to V.'s states and reactions to MS could be an effective control strategy. Observing and sharing her mental states allowed V. to be more relaxed at the end of the sessions. The sensation of "pulling out" her emotions was the sign of the defusion process activated

by V. towards her internal state, which V. perceived as positive and useful. Finally, some mindfulness-based strategies of emotional regulation and thoughts management, e.g., the "breath anchor" and the "here and now", were proposed to V., to regulate her symptoms and provide her with an increased sense of management.

Session 3

V. shares that she had acquired the mindfulness-based centering in the "here and now" and the "breath anchor" as a mantra because they helped her in managing emotions and thoughts and staying in the present every time her mind went to the future. Even if her anxiety about the future was often dominant, she reported less fatigue and better quality of sleep. Moreover, during the mindful moments, she could experience pleasure, freedom, bodily relaxation, and reduced fear, and her mind distracted from MS. V. found these results as encouraging.

We also focused on the importance of not trying to block or forget or remove internal contents, but, on the contrary, accepting, receiving, and integrating them with others. We shared that acceptance could be the middle ground between fight/control and resignation and it can provide mastery to V.

In this regard, V. referred that she could not accept the idea of being sick, because being sick was a significant threat to her. At the same time, she saw to be better able to manage the effects of this idea, such as her psychological symptoms. We worked together on differentiating between the objective events "MS" or "reduced health", and the subjective effects that they created in V. In this regard, we agreed that each of us has very little control over the objective life events, instead on our subjective reactions to them we have many more possibilities. Thus, V. could be the mistress

of her internal states and through managing them she could regain the control and freedom she felt she had lost. This awareness provided hope to V.

Meanwhile, we started to get curious about why her symptoms had appeared, about what significantly happened for V. with the MS, and which V.'s functioning had generated these reactions. Thus, we added the work of exploring the contents to the work of formal regulation of the symptoms. I proposed to V. the following homework: to collect, and writing them down, thoughts, emotions, and body sensations, as they would arrive during the week.

Session 4

V. reported having a head full of thoughts, anxiety, and tiredness, because of all the things she had to deal with. In this regard, she recognized that she was autonomous in doing things, not depending on anybody. This autonomy guaranteed her freedom, i.e., the freedom to do everything she desired. At the same time, we recognized that if everything depended on her, the cost she had to pay was heavy and characterized by burden, worries, others leaning on her, and a worse health state. Moreover, the more the cost was heavy, the more the need for support and security increased. Thus, we could see that autonomy guaranteed V. freedom, force, and the possibility of exploration. On the opposite, dependence could provide V. help from others, connection, and security.

This work stimulated V.'s system to recover connected memories. V. shared that when she was young, she searched for freedom, but she was very limited by her authoritarian parents. So, she married at a young age to obtain absolute freedom and autonomy from them.

We could also mentalize the emotions which moved V. between these two polarities (i.e., autonomy and dependence). Autonomy elicited anxiety and tiredness, while dependence was perceived by V. as a constraint: her worst nightmare was ending up in a wheelchair and completely losing her autonomy. Moreover, she felt boredom when she was too static, and boredom pushed her to seek stimuli. In this regard, V. felt that MS represented a threat to her freedom and autonomy, and she felt that as the disease progressed her freedom and autonomy would gradually decrease.

I noticed that V. seemed to be prevalently focused on the advantages that freedom guaranteed her. Thus, I explained to V. that each of our functioning has advantages but also disadvantages and I asked V. if searching for absolute freedom could have any costs. And V. shared that freedom had a very high price: V. had to marry very soon and became a mother very early, and this limited her and her exploratory needs.

Thus, at that point, we could see how both autonomy and dependence have their advantages and disadvantages. Moreover, they could probably complete and compensate each other: freedom provided V. exploration and exposition to stimuli, while dependence provided her security and less burden. For this reason, we shared that a functional way that could give her more balance could be using both polarities: experiencing dependence but maintaining freedom and experiencing freedom but also using dependence.

Finally, relative to the fact that MS invalided V.'s freedom, we shared that probably due to the disease progression, V.'s dependence would have increased. But both freedom and dependence could be intended in many ways. Thus, if freedom and dependence could be experienced in diverse ways, freedom would be maintained also in conditions of dependence, and vice versa.

Session 5

We shared mid-intervention monitoring and V. shared that the sessions transmitted her freedom and relaxation because they were clarifying, and her work was easier with the help of the therapist. V. also felt that all was going better: negative thoughts and emotions were still present, but she could easier let them go because she was learning to live with them. Moreover, her body sensations less alerted her and less generated fear: if she adverted some physical symptoms she did not immediately react like before, intending them as signals of a catastrophe, but she simply stayed, thinking "maybe it will pass". There was more space for hope and pleasant things. For example, the desire for traveling returned, while before for V. traveling was an impossible idea.

We resumed the topic of session 4, observing that V. felt dependence when she felt constrained by forced choices, while V. felt freedom when she did not feel any bonds.

Relatively to bonds, V. shared that the unique bond she had accepted with pleasure was the birth of her nephew. She loved taking care of him giving up many things. In this case, the constriction had never been a burden to her. Talking about him, V. said that "contributing to his growth had been a wonderful experience; we were both peaceful and we joined the pleasure to stay together". V. felt good with him and those spent together had been the best moments of her life.

Thanks to this V.'s insight, we had the occasion to see that constriction and dependence could also be a good experience. They could be an experience of realization, enrichment, satisfaction, and gratification, a warm relational experience, rich in affect. Thus, we could intend dependence as a connection and relationship. Dependence could not only mean receiving help from the other, but it could also mean sharing time with the other. Instead, freedom and autonomy could transmit

loneliness and affective dryness. Therefore, V. could be focused on her need to stay with others, e.g., her friends, and on the pleasure she could derive from the relationship.

At the end of the session, V. felt a sense of integration of different parts and strategies, instead of contradiction between them. V. was also surprised to have recognized that she could feel good also in unfree conditions. We shared that this was a powerful awareness, a protective resource that could open functional strategies against the disease progression. Depending on others could not be so bad as it was intended as relationship, love, enrichment, and help.

Thus, V. could face MS by developing a protective interpersonal network, but, at the same time, maintaining control and freedom of choice, by adapting to the illness in the "here and now", "moment after moment". For example, to continue to travel, she could identify local sanitarian centers or assurances that could help her in the case of necessity. Moreover, euthanasia could be intended not as the unique control strategy, but as the last control strategy that V. could use if she would encounter impossible physical conditions, but that could previously replace with other forms of control. So, euthanasia was the final way to maintain freedom if all the possibilities of autonomy would be lost. V. could not control the disease, but she could control her adaptation to it.

Session 6

V. better recognized that she felt distressed when she felt that all depended on her and when she found herself managing everything on her own. V. also better managed those moments of distress regulating emotions and bodily sensations, e.g., stopping the activities and having a walk or a break, with the effect of symptoms attenuation.

Concerning MS, she started to do the same: stopping thinking with worries about the future, but living and staying in the present with awareness, with the possibility to stay differently also in the most activating and tiring moments.

Relatively to negative thoughts, i.e., “future will be negative”, I showed V. mindfulness-based regulative strategies. One of them was the transformation of the thought, depowering it: we transformed V.’s negative thought “future will be negative” into the following progressive thoughts: “I think: “future will be negative”; “at this moment I think “future will be negative”; “at this moment the thought “future will be negative” arrives”. The effect of this transformation was that V. felt more hopeful about the future and acquired the awareness that she really could not know what her future would look like. Thus, she could say: “I do not know how my future will be; I must not wait for it, but I can stay in the present and live my present”. And V. said the same about MS: “I do not know how my disease will go, thus I can live the present, moment after m“ment, as it occurs".

Therefore, V. started to perform better management of symptoms and to function with more flexibility between the two polarities of autonomy and dependence, seeing their advantages and disadvantages and integrating them.

Sessions 7 and 8

We focused on the fact that the intervention was ending, and V. referred to be more calm, serene, and safe. She felt more degrees of freedom and possibility concerning MS: the winning strategy had been understanding how to see it and which strategies to activate to cope with it. And that was reassuring.

She was also more aware of her fear, and she perceived her fear as less impulsive and more controllable. V. continued to feel fear, but fear was less invasive, intense, and magnetizing.

V. shared that psychotherapy had been useful for her. She internalized the mantra "here and now" and she was training to do things with more emotional detachment and less involvement.

Recognizing to have these capacities and acquiring awareness of the fact that she could still function was a win for V.

V. also recognized that she tended to take care of her alone, and to ask for help after a lot of time. Acquiring awareness of this functioning let V. better manage this tendency and ask for help when she needed it.

Concerning how the intervention went, V. shared that we answered her initial questions and needs. The therapy represented for V. "a holiday from anxiety". She felt that the initial distress, weight on her shoulders, and pressure were not still present. She felt more inclined to functional coping and with more positive thoughts. For example, on the day of session 7 V. would have had the MS check-up, but she was not worried. She learned to live day by day, taking one thing at a time.

Finally, V. was a little sad about the end of the therapy because the therapy was reassuring for her. In this regard, we shared that in the future, in case of necessity, the service would be again at her disposal.

Conclusions

The psychotherapy performed for V. and with V. seemed to be effective because it favored V.'s more functional adaptation to MS. Moreover, it played a significant role

also respect to symptoms, which became less intense, less impactful, and more masterable. Finally, V. could increase the awareness of her internal functioning and more awareness provided her with more possibilities to change mechanisms and integrate new adaptive functioning into her system.

In the face of inescapable disease, moving the attentive focus from the disease to the patient opens to numerous possibilities to increase his quality of life regardless of how the disease goes. In this sense, psychotherapy is a lifetime opportunity for the individual that offers him a special relational place in which doing personal work on himself with the guidance of the therapist, characterized by aware observation and change.

For these reasons, cognitive-constructivist psychotherapy seemed to be effective also as a brief intervention. It can be declined into effective models of psychological interventions for patients affected by medical diseases, to be provided together with the other interventions needed by the individual, from a bio-psycho-social perspective of patients' care.

Further research on this type of psychotherapy with patients with medical diseases is desirable to bring further evidence for clinical practice.

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6 Patient-caregiver relationship

6.1 Article n. 6

Demoralization in family carers of patients with Mild Cognitive Impairment: a cross-sectional study.

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Submitted.

Abstract

Backgroud Mild Cognitive Impairment (MCI) can have an impact on carers' wellbeing. However, this is understudied.
Aims The study aimed firstly to assess demoralization in a sample of family carers of patients with MCI and to investigate its association with carers' burden, anxiety,

depression, and coping styles. Then, the study aimed to evaluate the association between carers' demoralization and patients' psychological and cognitive symptoms.

Methods The study was cross-sectional. Thirty-three patients with MCI and their family carers were included. Socio-demographic data were collected, and participants were asked to fill out a series of Italian validated scales assessing carers' demoralization, burden, anxiety, depression and coping, and patients' different types of distress and cognitive functions.

Results Carers' demoralization had a mean score of 24.39 (sd = 13.53) with higher mean scores in dysphoria and discouragement. It was associated with carers' burden, anxiety, and depression and seemed to be predicted by burden and depression. The "positive attitude" was a protective factor against demoralization. Demoralization was associated with patients' depression and short-term memory.

Conclusions Carers of patients with MCI can feel demoralization due to MCI-related significant changes such as uncertainty about the future, losses and alterations in roles and habits.

Moreover, both patients' cognitive deficits and patient-carer emotional reverberations could generate burden and depression in carers. When necessary, psychological support could favor carers' coping and alleviate their existential distress.

Keywords

Demoralization, carers, family carers, mild cognitive impairment, MCI

Introduction

Mild Cognitive Impairment (MCI) is a syndrome characterized by the presence of cognitive impairment greater than what is expected based on age and educational level [1]. MCI sometimes represents the prodromal phase of dementia and is generally associated with a worsening in the ability to learn new information or recall stored information [1].

Even though MCI does not interfere excessively with the normal activities of daily life [1, 2], its main characteristic, i.e., the cognitive deficit, may have a significant impact due to related feelings such as uncertainty of diagnosis, skill loss, change in social and family roles, embarrassment and shame, burden, frustration, and diminished self-confidence [3]. Moreover, patients with MCI frequently suffer from anxiety and mood disorders, which are probably due to their awareness of their cognitive problems [4, 5].

At the same time, the MCI clinical condition is different from dementia one and differences are detectable also relatively to caring. Great commitment and many resources are required for carers of patients with dementia, leading to a significant burden and increasing the risk of physical and psychological morbidity, e.g., reduced quality of life or higher rates of mortality, anxiety, and depression [6]. Moreover, these caregivers can be more distressed due to patients' condition, than the patients themselves [7]. Instead, carers of patients with MCI identify less with the caregiver role because of the reduced impact of MCI on daily functioning: they seem to have a fluid sense of caregiver identity with discontinuous self-identification [8]. At the same time, anticipatory grief and loss seem to be the main clinical aspect involving them: carers of patients with MCI can feel the loss of pre-existing relationships, control, and hope, and can be worried and uncertain about the future and their capacity to continue in caregiving the patient [8].

In this regard, demoralization can be defined as a syndrome characterized by existential distress, which can result from upsetting events or situations [9-12]. Failing the adaptation to these events can result in feelings of inability, uncertainty, hopelessness and helplessness, loss of meaning and purpose, and reduced self-esteem [10, 12-15].

The results of a recent study [16] on palliative care patients showed that demoralization can be present in both patients and carers. However, in the neurological field, the impact of an MCI patient's cognitive status on his carer's well-being is understudied [17]. Moreover, to our knowledge, to date no research investigated demoralization in carers of patients with MCI, despite MCI could elicit it.

Therefore, the present study aimed firstly to assess demoralization in a sample of family carers of patients with MCI and to investigate its association with carers' burden, anxiety, depression, and coping styles. Then, the study aimed to evaluate the association between carers' demoralization and patients' psychological and cognitive symptoms.

Methods

The study was cross-sectional. It was the complementary research of a primary research on psychological distress in patients with MCI.

Relatively to the statistical power of the study, considering the number of included variables, a sample size greater than 160 participants would ensure good power to the analyzes. The sample consisted of 33 pairs of patient-family carers. Participants were recruited at Neurology 1 Unit, Molinette Hospital, "Città della Salute e della Scienza" Hospitals of Turin. The research was proposed to the pairs during the hospitalization of the patients in the unit. Patients were hospitalized in the unit for one week to receive diagnostic exams and visits.

Inclusion criteria were aging over 18 and being a patient diagnosed with MCI or his family carer, understanding and speaking the Italian language, not being affected by any severe psychiatric or cognitive disorders, and not taking drugs preventing the provision of informed consent and the participation to the research. The diagnostic criteria for MCI involved: evidence of cognitive decline shown by a score between 23.7 and 27 on the Mini-Mental State Examination (MMSE) [18] (recruited patients' mean MMSE score = 24.4, sd = 3.8); preserved daily independence shown by low impairment in the instrumental activities of daily living (scores on Clinical Dementia Rating Scale = .5) [19]; and the absence of a diagnosis of dementia, a condition of delirium or mental disorder explaining the cognitive deficits [20-22].

All the participants provided informed consent. The study was approved by "Comitato Etico Interaziendale A.O.U. San Giovanni Battista di Torino A.O. C.T.O./Maria Adelaide di Torino": protocol number 0034410, procedure number CS2/1179, date of approval: 29/03/19.

Participants were asked to fill out a sheet collecting their socio-demographic data and a series of self-compiled Italian validated scales (see Tools section). Participants were asked to independently fill out the scales, but it was also allowed to receive the assistance of a study researcher.

Tools

Carers were administered with the Italian versions of the following validated scales:

- Demoralization Scale (DS) [23, 24], for the evaluation of the level of demoralization;
- Zarit Burden Interview (ZBI) [25, 26], for the assessment of the caregiving burden;
- Hospital Anxiety and Depression Scale (HADS) [27, 28], which assesses the presence of anxiety and/or depressive symptoms in the carer;

- Coping Orientation to Problems Experienced — New Italian Version (COPE-NVI) [29, 30], which evaluates the carer's coping strategies.

The following validated scales were administered to patients for the assessment of distress:

- Perceived Stress Scale (PSS) [31, 32], which assesses perceived stress over the past month;
- Beck Depression Inventory-II (BDI-II) [33, 34] which evaluates the severity of depression;
- State-Trait Anxiety Inventory (STAI) [35, 36] which evaluates state anxiety and trait anxiety;
- Demoralization Scale (DS) [23, 24] which provides an index of the patient's level of demoralization;
- Patient Dignity Inventory (PDI) [37, 38] which assesses distress related to the patient's sense of dignity.

The following neuropsychological tests were used to evaluate patients' cognitive performance:

- Mini-Mental State Examination (MMSE) [18, 39] which assesses cognitive impairment;
- Trail-Making Test (TMT) [40, 41] which assesses visual attention and task switching;
- Digit Span (DIG.SP) [42, 43] which evaluates short-term memory;
- Rey's 15-Word Test (RAVLT) [44, 45] which assesses verbal learning ability and memory.

- Frontal Assessment Battery (FAB) [46, 47] which tests some cognitive abilities controlled by the frontal lobes.

- Verbal Fluency Test for Phonemic Categories [48] which assesses the ability to evoke words.

- Test of Verbal Fluency by Semantic Categories [49] which evaluates the extension and usability of lexical heritage with semantic access.

The complete description of the tools is presented as a Supplementary File.

Data Analysis

Descriptive statistics such as means, standard deviations, and frequencies were performed. Associations between carers' demoralization and carers' burden, coping styles, anxiety, depression, and socio-demographic characteristics were investigated using Spearman's Rho correlation coefficient, Mann Whitney's U Test with independent samples, Kruskal Wallis's Test with independent samples, and multiple linear regression. Finally, the associations between carers' demoralization and patients' psychological and cognitive symptoms were assessed through Spearman's Rho correlation coefficient. All the test assumptions were verified. *P* values less than or equal to 0.05 were considered significant. Effect size of statistics, i.e., Cohen's categorization of correlation intensity and adjusted r^2 for regression models were considered.

SPSS Statistics Version 24.0 software (IBM Corp. Armonk, NY, USA) was used to execute the analysis.

Results

Carers' socio-demographic and clinical characteristics

Most of the carers were women (66.7%, n = 22) and married to the MCI patient they care for (60.6%, n = 20). 45.5% of carers (n = 15) were retired. See Table 1.

Demoralization had a mean score of 24.39 (sd = 13.53) with higher mean scores in dysphoria (mean = 5.85; sd = 3.15) and discouragement (mean = 9.36; sd =5.27) DS subscales.

Carers had moderate scores on ZBI (mean = 25.45; sd = 16.47), low scores on the "anxiety" HADS subscale (mean = 5.79; sd = 3.82), and low scores on the "depression" HADS subscale (mean = 5.48; sd = 4.35). See Figure 1. The COPE-NVI subscales with higher scores were positive attitude and orientation to the problem. See Table 1.

Associations between carers' demoralization and carers' other variables

Carers' demoralization total score was more highly associated with carers' burden, anxiety, and depression.

Regarding demoralization subscales, the strongest correlations were between all subscales of demoralization with burden, anxiety, and depression. See Table 2. The linear regression model identified carers' scores on ZBI, "depression" HADS subscale, and "positive attitude" COPE-NVI subscale as predictors of demoralization in carers. See Table 3.

Carers' demoralization was not associated with carers' socio-demographic variables.

Associations between carers' demoralization and patients' psychological symptoms

Carers' demoralization was more highly associated with patients' depression

Regarding demoralization subscales, the strongest correlation was between carers' discouragement and patients' depression. See Table 4.

Associations between carers' demoralization and patients' cognitive symptoms

Carers' demoralization was more highly associated with patients' short-term memory. Regarding demoralization subscales, the strongest correlation was between carers' sense of failure and patients' spatial planning capacity. See Table 4.

Discussion

The study aimed firstly to assess demoralization in a sample of family carers of patients with MCI and to investigate its association with carers' burden, anxiety, depression, and coping styles. Then, the study aimed to evaluate the association between carers' demoralization and patients' psychological and cognitive symptoms.

Relatively to the first aim, mild levels of demoralization were revealed in the carers who participated in our study. In MCI, "cognitive impairment must be noticeable, but not severe enough to significantly impact daily functioning" [8]. Thus, its effect on carers might be lower than that caused by a more serious disease, e.g., dementia or other neurodegenerative diseases. However, MCI can cause alterations in carers' well-being in terms of losses and worries [8]. Thus, carers can feel demoralization as a syndrome of existential distress due to significant changes and symptoms they experience. In this regard, dysphoria and discouragement were the two clinical subdimension of demoralization with higher scores. This data suggests emotional distress such as sadness, pessimism, guilt, irritability, regret, sense of loneliness, and the perception of feeling trapped by what happened as the psychological symptoms that MCI patients' carers may most develop.

Carers' demoralization was most associated with their burden and depression. The more the caregiver must assist the patient, the more existential distress is elicited. A greater cognitive impairment requiring more assistance could amplify the feelings of uncertainty about the future and fear for the disease progression and elicit demoralization. Moreover, carers' difficulties in adapting to the loss of previous lifestyles, habits, relationships, and possibilities, and the reduction of hope could generate both depression and demoralization, which might feed each other.

Relatively to coping, a positive attitude seems to be a protective factor against demoralization. A positive attitude refers to strategies of acceptance, containment, and positive reinterpretation of the events [30]. These strategies could favor the carer's adaptation to the patient's MCI and can reduce their sense of failure in coping.

Carers were more demoralized as patients were more depressed. Emotional reverberations between patients and carers can occur: patients with depression could have more difficulties in coping with MCI and their carers also seem to show more emotional concerns relative to coping ability.

Finally, carers' demoralization was related to patients' reduction of memory and spatial control capacities. Dysfunctions in short-term memory, executive functions, and visual-spatial perception are the most characterizing the MCI conditions and can be perceived by carers in everyday life, e.g., when patients are distracted, they do not answer questions or do not remember and require repetitions. Thus, they could elicit demoralization because carers can struggle in normally interacting with patients and because they are tangible signs of a new condition to face.

This evidence highlights the importance of supporting carers in their process of adaptation to patients' MCI. When appropriate and necessary, ad hoc psychological interventions on demoralization could alleviate their existential distress, promote the search for more functional coping strategies, and favor the establishment of new balances in the face of the stressful circumstances aroused by MCI.

The study has some limitations. The cross-sectional design prevented from observing changes in variables over time and did not provide clear data on causal relationships between variables. Moreover, the small sample size limits the evidence's strength. Finally, the low variability of the sample limits the representativeness of the study of the population of MCI patients' carers. Future studies could implement our findings through longitudinal designs or qualitative observations that should enrich our clinical evidence.

Conclusions

Carers of patients with MCI can feel demoralization, especially dysphoria and discouragement, due to MCI-related significant changes. Demoralization was associated with carers' burden, anxiety, and depression and seemed to be predicted by burden and depression. While the "positive attitude" coping style was a protective factor against it.

Demoralization was also associated with patients' depression and short-term memory. They could elicit demoralization because carers can struggle in normally interacting with patients and because they are tangible signs of a new condition to face.

Thus, carers can most feel emotional symptoms such as sadness, pessimism, guilt, irritability, regret, a sense of loneliness, and the perception of feeling trapped by what happened. Moreover, both difficulties in adapting to the MCI-related conditions and patient-carer emotional reverberations could generate burden and depression in carers. When necessary, psychological support could favor carers' coping and alleviate their existential distress.

Statements and Declarations

The authors did not receive any funding for the study.

The authors report there are no competing interests to declare.

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Tables

Table 1. Carers' socio-demographic and clinical variables (N = 33).

Socio-Demographic Variables		
	n	***%***
Gender		
Female	22	66.7
Male	11	33.3
Marital Status		
Married	23	69.7
Divorced	1	3.0
Cohabitant	5	15.2
Single	3	9.1
Missing	1	3.0
School Education		
High School Diploma	12	36.4
Middle School Diploma	9	27.3
University Graduation	9	27.3
Missing	3	9.1
Caregiving Relationship		
Spouse	20	60.6
Children	11	33.3
Partner	1	3.0
Another family member	1	3.0

Clinical variables		
	Mean	***Sd***
DS Total score	24.39	13.53
DS – Loss of meaning	2.33	3.51
DS – Dysphoria	5.85	3.15
DS – Discouragement	9.36	5.27
DS – Impotence	3.79	3.39
DS – Sense of failure	3.09	2.41
ZBI	25.45	16.47
HADS – Depression	5.48	4.35
HADS – Anxiety	5.79	3.82
COPE – Social support	27.27	7.19
COPE – Avoidance strategies	22.21	4.16
COPE – Positive attitude	33.00	5.81
COPE – Problem orientation	31.15	7.05
COPE – Trascendent orientation	21.45	5.25

Notes. N, absolute frequencies; %, percent frequencies; sd, standard deviation; DS, Demoralization Scale; ZBI, Zarit Burden Interview; HADS, Hospital Anxiety and Depression Scale; COPE, Coping Orientation to Problems Experienced

Table 2. Associations between carers' demoralization and carers' other clinical variables.

	ZBI ***r***	**HADS-Anxiety** ***r***	**HADS-Depression** ***r***	**COPE-Social support** ***r***	**COPE-Avoidance strategies** ***r***	**COPE-Positive attitude** ***r***
DS – Total score	.56**	.65**	.58**	.16	.36*	-.05
DS-Lost of meaning	.66**	.52**	.53**	.09	.38*	.02
DS-Dysphoria	.48**	.52**	.32	.37*	.27	.22
DS-Discouragement	.58**	.62**	.56**	.08	.31	-.01
DS-Impotence	.37*	.48**	.55**	-.00	.22	-.15
DS-Sense of failure	.00	.01	.00	-.01	.11	-.35*

Notes. R, Spearman's correlation index; *Significant at .05 level; **Significant at .01 level. DS, Demoralization Scale; ZBI, Zarit Burden Interview; HADS, Hospital Anxiety and Depression Scale; COPE, Coping Orientation to Problems Experienced; Intensity of correlations: $r < .4$, low; $3 < r < 6$, mild; $r > 6$, high.

Table 3. Carers' demoralization significant predictors

	B	β	F
Model 1			
Constant	9.96		28.14
ZBI	.567	.69	
Model 2			
Constant	5.66		30.94
ZBI	.41	.50	
HASD-Depression	1.50	.48	
Model 3			
Constant	22.76		25.11
ZBI	.47	.58	
HADS-Depression	1.34	.43	
COPE-NVI-Positive Attitude	-.54	-.23	

Notes. Summary of linear regression model: R^2= ,722 for Model 3; B = unstandardized regression coefficients, β = standardized regression coefficients; F = ANOVA test of the model.

Table 4. Associations between carers' demoralization and patients' psychological and cognitive symptoms.

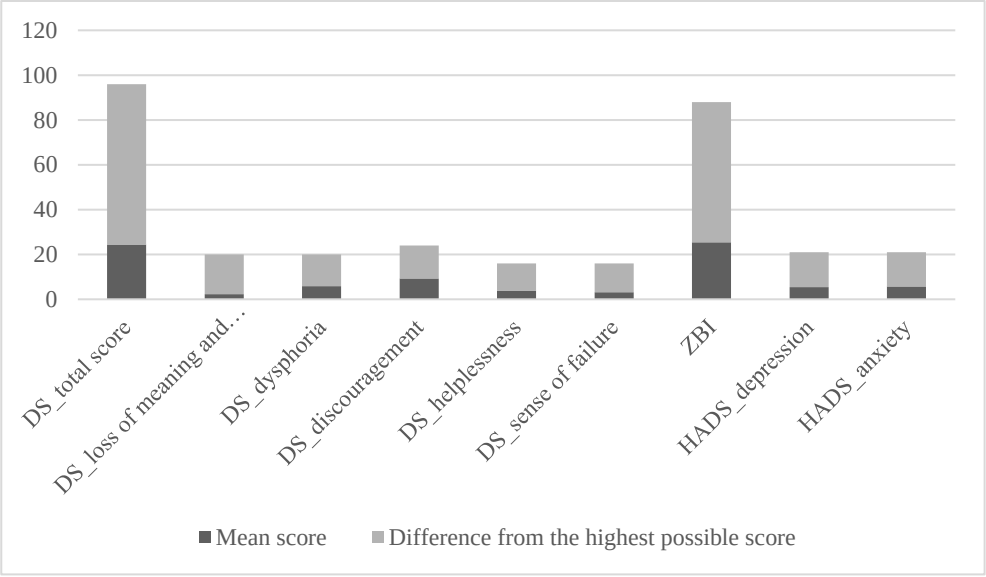
CARERS	**PATIENTS**						
		BDI ***r***	**BDI-Somatic-affective** ***r***	**DS-Dysphoria** ***r***	**TMT-A** ***r***	**TMT-B** ***r***	**DIG.SP.DIR.** ***r***
	DS	.34*	.31	-.45**	-.02	-.02	-.52*
	DS-Loss of meaning	.11	.10	-.17	-.09	-.19	-.45*
	DS-Dysphoria	.17	.17	-33	-.19	-.28	-.27
	DS-Discouragement	.40*	.39*	-.44**	-.12	-.02	-.53*
	DS-Impotence	.30	.25	-.41*	-.04	-.02	-.41

	DS-Sense of failure	.01	.00	-.16	-.59**	-.40*	-.01

Notes. R, Spearman's correlation index; *Significant at .05 level; **Significant at .01 level. DS, Demoralization Scale; BDI, Beck Depression Inventory; TMT, Trial Making Test; DIG.SP.DIR, Digit Span Direct. Intensity of correlations: r < .4, low; 3 < r < 6, mild; r > 6, high.

Figures

Figure 1. Carers' levels of demoralization, burden, anxiety, and depression (N = 33).



Notes. DS, Demoralization Scale; ZBI, Zarit Burden Interview; HADS, Hospital Anxiety and Depression Scale.

Supplementary File

Tools

Tests administered to caregivers:

- **Demoralization Scale (DS)** *(Kissane et al., 2004; Costantini et al., 2013)*, for the evaluation of the level of demoralization; The Demoralization Scale (DS), first developed by Kissane et al. (2004), covers five sub-dimensions: loss of meaning and purpose in life (5 items), dysphoria (5 items), discouragement (6 items), impotence (4 items), sense of failure (4 items). Each item is assigned a score ranging from 0 (never) to 4 (all times). In the original version of the scale, a total score is also taken into consideration, deriving from the sum of the scores assigned to the individual items.

- **Zarit Burden Interview (ZBI)** *(Zarit et al., 1980; Chattat et al., 2010)*, for the assessment of the caregiving burden. The Zarit Burden Inventory (ZBI) is an interview widely used to evaluate the consequences that the care burden of a family member with chronic or degenerative diseases has on the caregiver (Bédard et al., 2000). It is a tool that can be used both in self-report form and in the form of a structured interview (Zarit et al., 1980). It is made up of 22 items. It expects the caregiver to respond on a likert scale from 0 (never) to 4 (almost always) based on the degree of agreement she has with the individual items. The items investigate how the patient's disability impacts the caregiver's quality of life, psychological suffering, guilt, financial difficulties, shame, and social and family difficulties (Zarit et al., 1980). Consequently, the total score, which is calculated by adding the response scores to the single item, is between 0 which corresponds to a null care load, to a maximum of 88 which corresponds to a maximum level of

care load. Values below 20 indicate a minimal or no care burden. Values between 21-40 indicate mild to moderate load. Values between 41-60 indicate a moderate to severe care burden. Finally, values between 61-88 indicate a severe care burden (Zarit et al., 1980; Bétard et al., 2000).

- **Hospital Anxiety and Depression Scale (HADS)** *(Zigmond & Snaith, 1983; Costantini et al., 1999)*, which assesses the presence of anxiety and/or depressive symptoms in the caregiver. The Hospital Anxiety and Depression Scale (abbreviated: HAD Scale) is presented as a reliable tool for screening for clinically significant anxiety and depression in patients attending a general medical clinic. This scale has also been shown to be a valid measure of the severity of these mood disorders and thus repeated administration of the scale at subsequent visits to the clinic will give the clinician useful information on the trend (Snaith & Zigmond, 1983). HADS is a tool for screening anxiety and symptoms of depression in clinical practice, especially in the fields of somatic and psychosomatic medicine, it was originally designed for use in the hospital setting, it is applicable to all age groups from the age of 15 (Snaith & Zigmond, 1983). The tool, which takes 2-3 minutes to complete, is made up of 14 items on a Likert scale ranging from 0 (never) to 3 (very often) (of which 7 relating to anxiety and 7 relating to depression) (Snaith & Zigmond, 1983).

- **Coping Orientation to Problems Experienced - New Italian Version (COPE-NVI)** *(Carver et al., 1989; Sica et al., 2008)*, which evaluates the caregiver's coping strategies. The Coping Orientations to Problem Experienced (COPE) is a self-report questionnaire consisting of 60 items that takes into consideration different coping modalities (Carver et al., 1989;

Sica et al., 2008). The tool consists of 25 items which evaluate the following subscales: avoidance strategies, transcendent orientation, positive attitude, social support, and problem orientation. The questionnaire asks to evaluate how often the subject carries out - in difficult or stressful situations – the investigated coping process; there are four possible answers, ranging from "usually I don't" to "I almost always do". In the instructions it is emphasized that the subject should not refer to a specific stress but rather think about how he usually behaves in stressful situations (Sica et al., 2008).

Test administered to patients for the assessment of distress:

- **Perceived Stress Scale (PSS)** *(Cohen, 1994; Fossati, 2010)* which evaluates the perceived stress in the last month. It is the most used psychological tool to evaluate and quantify the perception of stress. It is a measure of the degree to which situations in one's life are rated as stressful. The total items are 10 on a Likert scale ranging from 0 (never) to 4 (very often) and were designed to assess how much the respondents find their life unpredictable, uncontrollable, and overloaded (Cohen et al., 1994). The scale also includes a series of direct questions about the patient's current levels of stress. The PSS was designed and validated on samples with at least a junior high school education (Cohen et al., 1994). The PSS questions concern feelings and thoughts perceived in the last month. In each case, respondents are asked how often they feel a certain way (Cohen et al., 1994).

- **Beck Depression Inventory-II (BDI-II)** *(Beck, 1967; Sica et al., 2007)* which assesses the severity of the depression. The BDI-II has 21 items on a 4-points Likert scale, ranging from not existent (0) to severe (3). Items include the following contents: (a) sadness, (b) pessimism, (c) past failure, (d) loss of

pleasure, (e) feelings of guilt, (f) feelings of punishment, (g) self-esteem, (h) self-criticism, (i) suicidal thoughts or desires, (j) crying, (k) agitation, (l) loss of interest, (m) indecision, (n) sense of worthlessness, (o) loss of energy, (p) altered sleep patterns, (q) irritability, (r) altered appetite, (s) difficulty concentrating, (t) tiredness or fatigue and (u) loss of interest in sex (Beck et al., 1996). The BDI-II is characterized by a two-factor solution (somatic-affective and cognitive). The BDI-II represents the most clinically used tool for the evaluation of depression (Beck et al., 1996).

- **State-Trait Anxiety Inventory (STAI)** *(Spielberg, 1989; Pedrabissi & Santinello, 1989)* which evaluates state anxiety and trait anxiety. The State-Trait Anxiety Inventory (STAI) (Spielberger, 1989) is a self-report measurement tool commonly used to assess state anxiety (through the S-Anxiety scale) and trait anxiety (with the T-Anxiety scale) through 40 items marked by a Likert scale (Spielberger et al., 1983). The S-Anxiety Scale (STAI Form Y-1) is made up of twenty statements that rate how respondents feel "right now, in this moment". The T-Anxiety Scale (STAI Form Y-2) is made up of twenty statements that assess how people generally feel (Spielberger, 1989).

- **Demoralization Scale (DS)** *(Kissane, 2004; Costantini et al., 2013)* which provides an index of the patient's level of demoralization. See the above description.

- **Patient Dignity Inventory (PDI)** *(Chochinov, 2008; Ripamonti et al., 2012)* which assesses distress related to the patient's sense of dignity. The Patient Dignity Inventory (PDI) (Chochinov et al., 2008) is one of the few tools

available to measure dignity, developed by Chochinov according to his dignity model for terminally ill patients (Chochinov, 2002; Chochinov et al., 2008). The PDI is made up of 25 items, each of which is rated on a 5-point scale ranging from 1 (not a problem) to 5 (it's a problem that overwhelms me). The instrument evaluates five subscales: symptom distress, existential distress, dependency, peace of mind and social support.

This questionnaire has been validated in many languages (Albers et al., 2011; Parpa et al., 2017), and has also been applied in unconventional contexts, such as cardiology units (Abbaszadeh et al., 2015) and seriously ill outpatient facilities (Chochinov et al., 2016). Validation studies demonstrated good internal consistency. The preliminary validation study in an acute psychiatric ward highlighted the three factors of PDI, which represented the main areas of dignity, excellent internal consistency, and statistically significant positive correlation with the Hamilton (1960) scales for both depression and anxiety (Di Lorenzo et al., 2017).

Neuropsychological tests used to evaluate patients' cognitive performance:

- **Mini Mental State Examination (MMSE)** *(Folstein et al., 1975; Frisoni et al., 1993)* which assesses cognitive impairment. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) is a widely used neurocognitive test for the evaluation of intellectual deficits and the presence of cognitive impairment (Folstein et al., 1975). It is a screening tool used to investigate the presence of dementia in subjects at risk, or neuropsychological syndromes of various kinds (Folstein et al., 1975). The MMSE it is made up of 30 questions that refer to seven main cognitive areas: 1) orientation over time; 2) orientation in space; 3) recording of words; 4) attention and

calculation; 5) re-enactment; 6) language and 7) constructive praxia. The overall score varies from a minimum of 0 to a maximum of 30 points. Scores ranging from 0 to 18 indicate the presence of severe impairment of cognitive abilities; a score between 18 and 24/25 indicates mild impairment; from 26 upwards there is a condition of normality. It is a test mainly built based on the symptoms of functional onset diseases (such as Alzheimer's disease); in a subject affected by a dysexecutive onset disease (such as Parkinson's disease) it may not show any deterioration, except at more advanced stages of the disease. The administration and interpretation of the results must always and only be carried out by a licensed physician or psychologist.

- **Trail-Making Test (TMT)** *(Reitan, 1958; Gaudino et al., 1995)* which assesses visual attention and task switching. The Trail Making Test (TMT) is one of the most popular neuropsychological tests and is included in most of the test batteries used to assess the neurocognitive functioning of patients (Tombaugh, 2004). TMT provides information on visual search, scanning, processing speed, mental flexibility, and executive functions. It was originally part of the Army Individual Test Battery (1944) and was later incorporated into the Halstead-Reitan battery (Reitan & Wolfson, 1985). The TMT consists of two parts. TMT-A requires the individual to draw lines that connect in sequence 25 encircled numbers distributed on a sheet of paper. Activity requirements are similar for TMT B except that the person must alternate numbers and letters (e.g., 1, A, 2, B, 3, C, etc.) (Tombaugh, 2004). The score on each part represents the amount of time required to complete the task (Tombaugh, 2004). TMT is sensitive to a variety of neurological disorders and processes (Tombaugh, 2004). TMT was found to

be useful in discriminating MCI, demented, and normal controls with respect to both time and errors (Ashendorf et al., 2008).

- **Digit Span** *(Wechsler, 1945, 1955, 1981, 1987; Spinnler & Tognoni, 1989)* which evaluates short-term memory. The Digit Span (Wechsler, 1945, 1955, 1987; Wechsler & De Lemos, 1981) is a verbal memory span (digit memory) measurement test. This test was used in Wechsler batteries: the Intelligence Scales (Wechsler, 1955, Wechsler & De Lemons, 1981), and the Wechsler Memory Scale (WMS and WMS-R) (Wechsler, 1945, 1987). The Digit Span consists of two different tests:

  1) Digits Forward, which consists in repeating digits forward.

  2) Digits Backward, which consists of repeating digits backward.

  The test consists of pairs of numerical sequences; the examiner reads the numerical sequence (one number per second), and when this is repeated correctly by the patient, the examiner moves on to the next one, which is longer than the previous one; and continues in this way until the subject fails to repeat the sequence or manages to repeat the last sequence consisting of 9 digits. Occasionally a third sequence is administered after two failures within the same couple. The 89% of normal subjects have a Digit Forward between 5 and 8 (Kaplan et al., 1991).

- **Rey's 15-Word Test (RAVLT)** *(Rey, 1958; Carlesimo et al., 1996)* which assesses verbal learning ability and memory. Rey's 15-word test is a neuropsychological test developed for the first time by Rey (1958) with the aim of assessing verbal learning ability and memory. This test covers an age range from 20 to 89 years, and the administration lasts from 10 to 15 minutes. It provides three parallel forms that minimize the learning effect in

the various repetitions of the test for monitoring the patient's neurocognitive function. The test shows high internal consistency scores (Ven den Burg, 1999), adequate test-retest reliability (Mitrushina & Satz, 1991), and poor learning effect (Mitrushina & Satz, 1991). Finally, Rey's 15-word test seems to have good ecological validity, especially regarding functioning in the daily life of patients with various disorders (Strauss et al., 2006).

- **Frontal Assessment Battery (FAB)** *(Dubois et al.,2000; Apollonio et al., 2005)* which tests some cognitive abilities controlled by the frontal lobes. The Frontal Assessment Battery (FAB) is a short widely used screening test, developed by Dubois et al., in 2000, which evaluates executive functions through cognitive and behavioral tests to test certain abilities controlled by the frontal lobes: classification, mental flexibility, motor programming, sensitivity to interference, inhibitory control and environmental autonomy. (Dubois et al., 2000; Moreira et al., 2017). It is a test battery consisting of 6 subtests:

  1) Analogies and conceptualization of similes, to evaluate the semantic categorization.

  2) Lexical fluency by phonemic category, to evaluate cognitive flexibility.

  3) Motor sequences that the subject must reproduce with the preferential hand, to evaluate praxia and motor programming.

  4) Response to instructions of a conflicting nature, i.e., inverted motor sequences in which the subject must reverse the gestures performed by the examiner, to assess the sensitivity to interference.

  5) Go-no go-task in which the subject must sometimes imitate the gestures presented by the examiner, other times inhibit the imitation program, to evaluate the inhibition control.

6) Inhibition of gripping behaviour, to evaluate environmental autonomy.

The subject is asked to perform all 6 tests; each test has a score that can vary from 0 to 3 (range 0-18). The FAB is a quick and easy to administer screening battery, which takes a time of 10 minutes (Dubois et al., 2000; Moreira et al., 2017). FAB is useful in the differential diagnosis of neurological diseases (Hurtado-Pomares et al., 2018) including Parkinson's disease, cortico-basal degeneration, frontotemporal dementias, Alzheimer's disease, Huntington's disease, supranuclear palsy progressive, and dementia with Lewy bodies (Moreira et al., 2017).

- **Verbal Fluency Test for Phonemic Categories** *(Novelli et al., 1986)* which assesses the ability to evoke words and **Test of Verbal Fluency by Semantic Categories** *(Spinnler & Tognoni, 1987)* which evaluates the extension and usability of lexical heritage with semantic access. The Verbal Fluency test allows a quick and efficient assessment of the ability to evoke words and often this test is an integral part of the test for aphasia as in the case of the MAE (Multilingual Aphasia Examination) (Benton & Hamsher, 1989) and the BDAE (Boston Diagnostic Aphasia Examination) (Borod et al., 1980). Verbal Fluency tests use phonological or semantic stimuli. For the phonemic categories, the letters P, F and L are presented as stimuli (Novelli et al., 1986). For the semantic categories the stimuli are given by colours, animals, fruits, and cities (Spinnler & Tognoni, 1987). In the verbal fluency test by letters, the examiner asks the patient to list as many words as they can think of (verbs, adjectives, nouns) with a specific letter of the alphabet, except for proper names of persons or cities, and derivatives. The patient has one minute. The total score is given by the sum of the words produced for each letter (Novelli et al., 1986). In the fluency test by semantic

categories, the examiner asks the subject to produce as many words as possible belonging to one of the semantic categories to be examined: colours, animals, fruits, and cities. The time available to the patient is always one minute. The methods of administering the test and recording the scores are like those of the fluence test by phonemic categories (Spinnler & Tognoni, 1987).

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6.2 Article n. 7

Attitudes towards and application of the Westeneng and colleagues' prognostic model for amyotrophic lateral sclerosis: an Italian survey.

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Introduction

Amyotrophic Lateral Sclerosis is a neurodegenerative disease characterized by progressive weakness of voluntary muscles due to motor neurons death in the brain and spinal cord. To date it is considered a system disease and non-motor symptoms may also be present, including cognitive and behavioural impairment. Muscle weakness progresses spreading from the site of onset and death generally occurs within 2-4 years of diagnosis from respiratory failure, although survival can be extremely variable, ranging from several months to more than 10 years. This phenotypical heterogeneity may have an impact on clinical care, because patients, caregivers and physician may be unable to adequately anticipate the timing of future

needs, and in parallel may have a negative impact on trials, which are often inefficient due to the lack of a proper stratification of the patients. In this scenario, the usefulness of a reliable prognostic tool is evident, firstly to provide tailored care and trial design, and also facilitate informed decision-making allowing the patients and families to plan the end-of-life care. Up to about 35 prognostic models for ALS have been proposed in the last decades (Su XW etal., 2013; Magnus et al., 2002; Taylor AA et al., 2016; Ong et al., 2017; Westeneng and coll., 2018), however, most of them showed limitation in modelling methodology with high risk of bias (Xu et al., 2021). Among these, the model proposed by Westeneng and coll. (2018) showed a low risk of bias and a good predictive performance and is based on 8 predictors: age at onset, FVC, diagnostic delay, ALSFRS-R slope, bulbar-onset, definite ALS, presence of fronto-temporal dementia and c9orf72 expansion. Noteworthy, based on this model, an online prediction tool called ENCALS Survival Model is already available for physicians. Due to its characteristics the model is nowadays widely used in both basic and clinical research and it is definitely useful for estimating patients' prognosis. Nevertheless, its application in the clinical practice may be more complicated due to, for example, cultural, spiritual, personal aspects dealing with the prognostic communication and more debate over the theme could be relevant. Therefore, the aim of the present study was to open this discussion through the investigation among Italian neurologists with experience on ALS of their knowledge of this model, the frequency of their use of the model in neurological practice and their general and spiritual attitude toward prognostic communication.

Methods

The study was cross-sectional. An anonymous online Survey, created using the platform MEDCap (www.medcap.unito.it) was conducted from may 2021 to march

2022. An email invitation to complete an electronic form of the Survey was addressed to Italian Neurologists with expertise in ALS and members of the MND Study Group of Italian Society of Neurology. The Survey was composed of 16 YES or NO questions (Table 2). Specifically, the questions concerned: the knowledge of this model among neurologists, the frequency of its use in neurological practice, the perception of the neurologists of the usefulness of this prognostic model for physicians, patients and caregivers. Further points explored by the Survey were participants' spiritual attitude, their general attitude toward prognostic communication, their perception of the eventual risk related to a prognostic communication in ALS patients, and the possible effect of this communication on the therapeutic alliance.

The survey was anonymous and based on voluntary participation, thereby protecting participants' personal data. The inclusion criteria were being an Italian citizen, being aged 18 or over, speaking Italian, and being a neurologist with expertise in ALS. The people who received the survey could firstly read the information on the research. Then, through the first question of the survey, participants declared to meet the inclusion criteria and provided their informed consent. Then, they could fill in the survey. If any information were needed and to receive the outcomes of the research, participants could contact C.M., the person responsible for this research study.

Data provided by respondents were collected in the online platform and exported for statistical analysis.

Statistical Analysis

Descriptive statistics (mean, range for dimensional data and proportions for dichotomous data) were used to summarize the results. Categorical variables were reported as percentages and Chi-squared test was used to compare groups. Levene's test was used to compare variance, and Student t-test was used to compare means.

The level of statistical significance was set at $p<0.05$. Data were analyzed using the Statistical Package for Social Sciences Version 26.0.0 (Statistical Package for Social Science, IBM Corp. Armonk, New York).

Results

Participants' socio-demographic characteristics

Most of participants were female (n = 19, 51.4%) and working in hospital (n = 21, 56.8%). The average age of the sample was 44.7 (sd = 12.1). Participants were specialist in neurology from average 15 years (sd = 12.7), dealing with ALS from the same years (mean = 14.9, sd = 9.6). Most of participants prevalently perform clinical work and have never received specific trainings on ALS (n = 23, 62.2%), on palliative care (n = 28, 75.7%) and on the patient-physician communication (n = 29, 78.4%). See Table 1.

Participants' spiritual aspects

The adherence to a religious cult was few important for most of participants (29.7%, n = 11), while spirituality was considered very important for the major of the sample (51,4%, n =19). Both religion and spirituality were practice only at times by most of participants (respectively 38.9%, n =14 and 48.6%, n=18). Finally, most of participants declared to explore patients' value system (i.e., believes, values, ideals, etc.) sometimes or often (64.8%, n =24).

Participants' attitudes towards prognostic communication

Most of participants declared to be required to carry out the diagnostic communication (97.3%, n =36) and that they ask patients/caregivers what and how much they want to know about patients' clinical condition (77.8%, n =28). Instead,

the major of the sample only sometimes asked patients if they wish to receive prognostic information (47.2%, n =17). Most of participants declared that patients (47.2%, n =17) and caregivers (55.6%, n =20) very often asked them prognostic communication. Over one third of the sample felt difficulties in talking about prognosis principally due to patients' low cultural background, dysfunctional reaction to diagnosis and low social support (38.9%, n =14).

Participants' use of the personalized prediction model by Westeneng and colleagues (2018)

Most of participants knew Westeneng et al.'s prediction model (73%, n =27). Over half of them did not or had never used the model (55.6%, n =15). Most of the minority who used it, used it with research aims (81.8%, n =8). Most of participants never communicated the existence of the model to patients (77.8%, n =21) and caregivers (77.8%, n =21) and never communicated the results of the model to patients (92.6%, n =25) and caregivers (96.2%, n =25). At the same time, over half of them did not have any fears relatively to the communication of the results of the model (61.5%, n =16).

The principal concerns hindering the use of the model expressed by the sample were the unreliability of the prediction and its disregard of individual variability, patients, and caregivers' inability to understand and manage the results of the model and the fear of traumatizing the patient. Moreover, almost half of the respondents believed that patients' characteristics – e.g., their personality traits, sociocultural background, level of acceptance of the illness, and cognitive impairment – can obstacle the clinician's use of the model (46.2%, n =12).

On the contrary, most of participants considered the model useful for the medical practice (89.2%, n =33), principally because it could improve patients' clinical management, the care planning, and the follow-up, it is useful to estimate patients'

prognosis and to support the clinician, and it could improve the clinician-patient communication.

Most of participants considered the model useful for patients (67.6%, n =25) and caregivers (75.7%, n =28), principally because it let them to plan and master their end-of-life, to increase their awareness of the disease impact, and to have specific information of the clinical condition and survivorship. For similar reasons, most of participants were in favor of the communication of the results of the model to caregivers (56.8%, n =21). On the contrary, the remaining participants highlighted the possible negative impact of the prediction on them, and the fact that the model could make the clinician-patient communication too rigid and too little gradual and does not provide certain prognostic information. For similar reasons, most of participants were not in favor of the communication of the results of the model to patients (62.2%, n =23) and considered the communication of the results of the model risky (54.1%, n =20). However, the clinician-patient relationship, the disease acceptance and patients' characteristics can mediate risks.

Most of sample believed that the communication of the results of the model cannot influence the therapeutic alliance with patients (62.2%, n =23). Who leaned towards a negative influence attributed it to its emotional impact both on patients and clinicians, to patients' hope reduction and to the decrease of patients' compliance to treatments.

Finally, most of participants shared that knowing the result of the model could favor themselves in care plan (81.8%, n =30), and patients and caregivers in life manage and plan (respectively 51.4%, n =19 and 65.8%, n =25). The principal reasons were the contribute of the model to the personalization of the multidisciplinary care plan, the possibility it offers to provide interventions at more adequate timing, and its role in improving patients' end-of-life management. See Table 2.

Associations between the use of the personalized prediction model by Westeneng and colleagues (2018) and the other considered variables

Participants who knew the model (t= .23, $p \leq .05$, Δ means = .54) and who had fears relative to the communication of the results of the model had on average more frequent spiritual practice (t= .37, $p \leq .05$, Δ means = .71).

Participants who considered the communication of the results of the model as risky (t= .49, $p \leq .05$, Δ means = .60) and who believed that the model could favor patients (t= .13, $p \leq .05$, Δ means = .72) had more frequent religious practice.

Participants who believed that the model could favor patients (t= .22, $p \leq .05$, Δ means = .77) and caregivers (t= .33, $p \leq .05$, Δ means = .94) were those who on average asked patients if they would like to receive prognostic information with high frequency.

Participants who more frequently asked patients if they would like to receive prognostic information, had more fears relative to the communication of the results of the model (χ^2= .02) and were less in favor of communicating the outcome of the model to caregivers (χ^2= .02).

Participants who had more difficulties in talking about prognosis less knew the model (χ^2= .001) or more believed that communicating the model results was risky (χ^2= .05).

Discussion

The results of the survey highlighted that prognostic communication is a complex process that should be personalized and tailored for each patient and his subjective condition. Thus, according to most of participants, also the use of the prediction model by Westeneng and colleagues (2018) might be adapted case by case, and its equal use for all a priori may not be effective. For example, this type of communication could be more adequate in certain phases of the disease rather than

in others. In this regard, participants considered also useful to evaluate the risk factors that play a role in the adaptation to this type of communication.

Furthermore, the prognostic communication is a significant moment that should be carefully prepared by asking the patient what and if he wants to know and offering emotional support before and after the communication if necessary. For this reason, multidisciplinary work that manages the different aspects of communication is of fundamental importance.

Relatively to the use of the model, results showed that, despite a good knowledge of the model, most of the participants never used the model in the clinical practice and did not communicate its existence and its results to the patients. Moreover, most of the neurologists only sometimes asked the patients if they want to receive prognostic information, while many patients and caregivers ask for this information. Thus, in the Italian scenario, neurologists seem not to be so favourable to the use of the model for the clinical practice, especially due to model limitations and fear of traumatizing patients. In this sense, it could be useful to personalize the use of the model on a case-by-case basis and to integrate medical care with psychological support to support prognostic communication.

It also emerged that the model seems to have the important advantage to help physicians, patients, and caregivers in the care and life planning. Thus, it seems to be desirable not its non-use, but its personalized and integrated use.

Moreover, there may be physicians' personal difficulties or few trained communication capacities that interfere with the communication process. So, adequate training and psychological support should be guarantee to physicians too.

Evidence suggest that the physician-patient therapeutic alliance is a factor that is not negatively affected by using the model with patients. Thus, the therapeutic alliance could be a protective factor to be addressed that could support the communication of the results of the model.

Finally, physicians' spirituality and positive attitude towards the prognostic communication could favourably mediate the use of the model, making it more appropriate and personalized. On the contrary, personal resistance towards difficult communications and the end of life seem to limit the knowledge and use of the model. Thus, cultivating one's own inner spiritual dimension and training oneself in emotionally dealing with death, illness, and limitations are psychological aspects that can play a significant role in using useful medical models as Westeneng and colleagues' one.

Future investigations on the theme should propose European surveys that investigate the cultural aspects of the different realities of the continent that could influence the use of the model.

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Tables

Table 1. Socio-demographic characteristics of the sample (N = 37).

Socio-demographic characteristics	***N***	***%***
Sex		
Female	19	51.4
Male	18	48.6
Age		
Mean	44.7	
Standard deviation	12.2	
Min	29	
Max	68	
Workplace		
Hospital	21	56.8
University	15	40.5
Socio-welfare residence	1	2.7
Years being a neurologist specialist		
Mean		
Standard deviation	15.0	
Min	12.2	
Max	1.0	
	42.0	

Years dealing with ALS		
Mean	14.9	
Standard deviation	9.6	
Min	2.0	
Max	40.0	
Percentage of work dedicated to clinical practice		
Mean	61.4	
Standard deviation	19.1	
Min	20.0	
Max	100.0	
Percentage of work dedicated to research		
Mean	36.0	
Standard deviation	16.5	
Min	0.0	
Max	70.0	
Having received a specific training on ALS		
Yes	14	37.8
No	23	62.2

Having received a specific training on palliative care		
Yes	9	24.3
No	28	75.7
Having received a specific training on patient-physician communication		
Yes		
No	8	21.6
	29	78.4

Table 2. Participants' use of the personalized prediction model by Westeneng and colleagues (2018)

QUESTIONS	**YES** n(%)	**NO** n(%)
1. Did you know the predictive model by Westeneng and colleagues (2018) before now?	27(73.0)	10(27.0)
2. Do you use or have you ever used the predictive model?	12(44.4)	15(55.6)
3. Have you ever notified your patients about the existence of the predictive model?	6(22.2)	21(77.8)
4. Have you ever communicated the result of the predictive model to your patients?	2(7.4)	25(92.6)
5. Have you ever notified your patients' caregivers about the existence of the predictive model?	6(22.2)	21(77.8)
6. Have you ever communicated the result of the predictive model to your patients' caregivers?	1(3.8)	25(96.2)
7. Are you worried about communicating the outcome of the predictive model to patients or caregivers?	10(38.5)	16(61.5)
8. Is there something hindering you from sharing the possibility of using the predictive model with patients or caregivers?	14(53.8)	12(46.2)
9. Are there any characteristics of the patients that hinder you from sharing the possibility of using the predictive model with patients or caregivers?	12(46.2)	14(53.8)

10. Do you think this predictive model could be useful for the physician?	33(89.2)	4(10.8)
11. Do you think this predictive model could be useful for the patient?	25(67.6)	12(32.4)
12. Do you think this predictive model could be useful for patient's caregiver?	28(75.7)	9(24.3)
13. Are you in favour of communicating the result of the predictive model to patient?	14(37.8)	23(62.2)
14. Are you in favour of communicating the result of the predictive model to patient's caregiver?	21(56.8)	16(43.2)
15. Do you think that the communication of the result of the predictive model could be risky?	20(54.1)	0(0.0)
16. Do you think that the communication of the result of the predictive model to the patient can influence the therapeutic alliance with him/her?	14(37.8)	23(62.2)
17. Do you think that knowing the result of the model can facilitate you in the assistance and planning of interventions (e.g. frequency of visits, timely palliative activation, pneumological check-ups)?	30(81.1)	7(18.9)
18. Do you think that knowing the result of the model can facilitate the patient in the management and planning of his own life?	19(51.4)	18(48.6)
19. Do you think that knowing the result of the model can facilitate patient's caregiver in the management and planning of his own life?	25(65.8)	13(34.2)

Notes. Questions n. 2-9 were answered only by participants who knew the predictive model by Westeneng and colleagues; n, absolute frequencies; %, percent frequencies.

7. Discussion

Different evidence emerged from the studies of my PhD project.

Firstly, more clarity has been made on the reasons why anxiety and depression could affect AD patients. These could arise in the early stages as a psychological reaction to the disease and due to difficulties in the adaptation to AD. At the same time the neurodegeneration of areas and circuits dealing with emotions can elicit the anxious and depressive symptoms, and, during the late AD stages, the serious cognitive impairment reduces the emotional responses and their expression. Moreover, anxiety and depression seem to be more intense in early-onset AD, due to the major impact of AD on the individual. Respect to this topic, further research, especially with longitudinal design and investigating involved psycho-social factors, would better clarify the comorbidity between depression, anxiety, and AD.

Relatively to MCI, patients with MCI can experience mild demoralization symptoms, especially discouragement and dysphoria, albeit in a mild form. And demoralization seems to be predicted by depressive symptoms. Psycotherapeutic interventions could favor patients with symptoms in the search for functional ways of adapting to MCI.
Different forms of psychological distress have been observed also in patients with MS as an effect of the MS diagnostic communication. These symptoms can be post-traumatic symptoms, anxiety, depression, and demoralization, and they can remain almost unchanged during the first year following diagnosis. Moreover, psychological distress was associated with dysfunctional coping, higher fatigue, worse quality of life, and worse cognitive functions. Thus, implementing distress management interventions that could reduce the impact of distress on patients' general well-being is fundamental. In this regard, psychological interventions could be effective in promoting functional coping and regulating symptoms. Furthermore,

taking care of the psycho-social aspects of communication and adequately supporting patients after diagnosis contributes to preserving patients' psychological well-being. More evidence is needed on this topic.

About interventions, AT resulted as a valid non-pharmacological option for patients that can guarantee interesting positive psychological and physiological effects. In particular, it seems to favour a more functional adaptation to the disease, improving symptoms and quality of life, and contributing to rebalancing the mind-body system. Further research is needed to bring reliable evidence to support even more the application of AT to medical conditions, especially the neurodegenerative ones. Also the cognitive-constructivist psychotherapy performed for the patient with MS seemed to be effective. It favored patient's more functional adaptation to MS and it made symptoms less intense, less impactful, and more masterable. Further research on this type of psychotherapy with patients with medical diseases is desirable to bring new evidence for clinical practice.

With respect to patient-caregiver relationship, it emerged that carers of patients with MCI can feel demoralization due to MCI-related significant changes. Demoralization was associated with carers' burden, anxiety, and depression and seemed to be predicted by burden and depression. While the "positive attitude" coping style was a protective factor against it. Thus, when necessary, psychological support could also favor carers' coping and alleviate their existential distress. Further research could better investigate the causes of occurrence of carers' distress.

Finally, about ALS, the project evidenced that psychosocial factors also deal with prognostic communication, that is a complex process that should be personalized and tailored for each patient and his subjective condition. Regarding the communication of the prognosis, the prediction model by Westeneng and colleagues (2018) seems to have the important advantage to help physicians, patients, and caregivers in the

care and life planning. At the same time, it could be useful to personalize the use of the model on a case-by-case basis, also assessing risk factors, and to integrate medical care with psychological support to support prognostic communication. Moreover, there may be physicians' personal difficulties or few trained communication capacities that interfere with the communication process. So, adequate training and psychological support should be guaranteed to physicians too. Finally, cultivating one's own inner spiritual dimension and training oneself in emotionally dealing with death, illness, and limitations are psychological aspects that can play a significant role in using useful medical models as Westeneng and colleagues' one. Future investigations on the theme should propose European surveys that investigate the cultural aspects of the different realities of the continent that could influence the use of the model.

8. Conclusions

The numerous and different evidence emerged in the presented articles seem to converge towards a unique possible direction of theorization of the person affected by a medical disease: the complexity.

The clinical observation and intervention must necessarily consider both the objective plan of the disease and the subjective plan of the illness and of the person's illness experience. The patient is a human being, social and relational for definition, self-organized according to his internal functioning, who lives experiences in an embodied way, through cognition, emotions, and body. For this reason, to abstract the medical disease from him results to be an impossible and failing operation, due to the multiple interactions and overlaps between psyche and soma and between the disease and the person who lives that disease.

For these reasons, keeping a broader view on the person that includes the attention to all the biopsychosocial aspects that characterize his experience, and their interaction is fundamental to really understand his clinical condition and effectively act to his aid.

A final published article is reported because it contains theorical and clinical reflections on psyche-soma dichotomy and its actual appropriateness that well represent the key to read and interpret my thesis, the common thread that links each other the presented articles, and the complexity from which we cannot escape.

8.1 Article n. 8

Is psyche-soma dichotomy still clinically appropriate?

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Abstract

This article proposes a historical re-contextualisation of the mind-body relationship and offers some evidence-based considerations concerning the current clinical appropriateness of psyche-soma dichotomy and psychosomatics.

The debate concerning the relationship between the mind and the body has a long medical, philosophical, and religious history, with psyche-soma dichotomy and psychosomatics alternating as the dominant clinical approach, depending on the prevalence of cultural orientations at different times. However, both models simultaneously benefit and limit clinical practice.

The neurosciences have reduced the gap between diseases of the psyche and the soma, which can now be seen as overlapping and having a common pathogenesis. Diseases should also be considered as illnesses by taking into account all of their biopsychosocial aspects in order to avoid therapeutic failures due to only partially

effective or ineffective interventions. Patient-centred care integrated with guideline recommendations may be the best means of uniting the psyche and the soma.

Key words: Psychosomatic medicine; mind-body medicine; biopsychosocial models.

Introduction

The debate concerning the relationship between the mind and the body has a long medical, philosophical, and religious history, with psyche-soma dichotomy and psychosomatics alternating as the dominant clinical approach depending on the prevalence of cultural orientations at different times. The view of the unity or division of the psyche and soma has varied from the holistic medico-philosophical approach of ancient Greece to the "biologisation" of the psychic aspects of scientific medicine.

This article proposes a historical re-contextualisation of the mind-body relationship and offers some evidence-based considerations concerning the clinical appropriateness of the different views.

Historical background

When proposing his humoral theory in ancient Greece, Hippocrates (IV century BC) tried to provide a unitary conception of human beings in which the body, mind and the environment were strictly interconnected. Centuries later, in 1662, Descartes replaced this perspective with his reflections on *res extensa* (the domain of science) and *res cogitans* (the domain of philosophy and theology) as a means of freeing science from religious influences [1]. However, this was certainly not a real dichotomy as he wrote "*Inputs are passed on by the sensory organs to the epiphysis in the brain, and from there to the immaterial spirit"* [1]. Unfortunately, posterity

misunderstood the difference between *res extensa* and *res cogitans*, thus leading to the cultural and medical exclusion of *res cogitans* that has persisted ever since.

The biomedical model, that developed during the XIV century on the basis of the principles of reductionism and mind-body dualism, is still accepted today. It relates symptoms to pathophysiological mechanisms, which therefore become treatment targets, and attributes less importance to the subjective experiences of the individual. Treatments are not tailored to the patient, and patients are simply required to adhere as closely as possible to what is prescribed. Furthermore, the biomedical model also relates psychiatric symptoms to organic factors, as can be seen in Wilhelm Griesinger's 1868 assertion that "*Mental disease is brain disease*" [2].

The biomedical model favoured the study of human anatomy and has led to fundamental medical developments, but it runs the risk of ignoring symptoms that cannot be explained by physiological mechanisms and the scientific method, such as some psychological or psychiatric symptoms, or psychosocial factors influencing medical conditions.

This changed with the introduction of psychosomatics [3]. The word "*psychosomatic*" first appeared in the medical literature in an article published in 1818 by Johann Christian August Heinroth (1773-1843) [4], the first professor of Psychology at the University of Leipzig. He was the leader of the "Psychiker" school, which suggested that consideration of the mind was essential when treating illness, unlike the "Somatiker" school, which maintained that mental disorder was caused by bodily disease [5].

At the beginning of the XX century, there was a *rapprochement* between the philosophies of phenomenology (Edmund Husserl) and hermeneutics (Martin Heidegger) and the psychology of Wilhelm Wundt (1896), and psychiatrists such as Karl Jaspers and internists such as Viktor von Weizsäcker, also greatly influenced the development of psychosomatic medicine.

It was in this cultural context that Sigmund Freud (1856-1939) pronounced his famous statement: "*The ego is first and foremost a bodily ego. It is not merely a surface entity but is itself the projection of a surface. If we wish to find an anatomical analogy for it, we can best identify it with the 'cortical homunculus' of the anatomists, which stands on its head in the cortex…*These words marked the beginning of the recognition of many clinical and theoretical examples of interactions between the mind and body, and psychoanalysts proposed that people who had difficulty in expressing rage can release their tensions at somatic level: i.e. unconscious factors may be relevant to the genesis of disease states.

Subsequently, disciples of Freud such as Franz Alexander (1891 – 1964) contributed to the study of somatic diseases that could be related to emotional factors, such as inflammatory bowel disease, peptic ulcer, hypertension, asthma, rheumatoid arthritis, eczema, etc., thus promoting an interdisciplinary scientific approach to the study of man [3] and leading to the founding of scientific journals such as Psychosomatics (the journal of the Academy of Psychosomatic Medicine) in 1939 or Psychosomatics and Medical Psychology in 1948.

Finally, Roy Grinker coined the term *biopsychosocial* in 1954, and used it in his article entitled *"A struggle for eclectism"* to urge psychiatrists to incorporate advances in biology in their models rather than relying purely on psychoanalytic dogma [6]. Some years later in 1977, on the basis of the 1907 statement of Ludolf Von Krehl that "*We do not treat diseases, but sick people",* George Engel advocated the adoption of a new medical model that had a more comprehensive approach to patients: the *biopsychosocial model (BPSM).* In his opinion, "*it is essential to know who the patient is, as well as what disease he has*" if we want to avoid treating a disease without considering the peculiarities of the person involved. In this sense, he began to emphasise the psychosocial aspects of illness, which must be seen as a result of interacting mechanisms at cellular, tissue, organic, interpersonal, and environmental levels [7].

The BPSM opened the transition from a disease framework that reflects the biomedical perspective of analysing symptoms and signs in order to formulate a diagnosis and prescribe specific treatments, to an illness framework based on the patient's perspective of his disease, which has the purpose of investigating the subjective experience of illness, and is characterised by beliefs, emotions, perceptions, feelings, expectations, and adaptations. The BPSM integrates the biological and psychosocial aspects of the process of care. Grinker applied it to psychiatry to emphasise *"bio"* against psychoanalytic orthodoxy; Engel applied it to medicine to emphasise *"psychosocial"* against the biomedical approach.

The BPSM was partially ostracised by the medical journals that were more susceptible to the biomedical reductionism that simplifies treatments and neglects individual responses, something that was already going against clinical experience [8-10].

Today's clinical practice: the bio-medical or biopsychosocial model?

It is now well established that illness is a complex experience that is not always exclusively somatic or exclusively psychic perspective but can only be understood by considering multiple perspectives. Among the many examples of the psyche-soma overlap, peptic ulcer disease has long been considered a classic psychosomatic illness, but it is often sustained by *Helicobacter pylori* and can only be cured by a therapeutic approach that addresses both its biological and psychological causes.

The bio-medical model may be limited in its approach to patients as can be seen in the case of medical guidelines, which are essential for ensuring that clinicians correctly use medical treatments, but cannot be applied in an undifferentiated manner, without considering the possible need for adaptations to individual cases. A drug can induce different genetic, metabolic, behavioural, or social responses that need customised adjustments in terms of choice, dose, titration, and so on. Even if a treatment is correctly proposed on the basis of guidelines, it must be tailored to

psychological and environmental parameters: for example, fear of the drug, due a previous negative experience, may give rise to a nocebo effect that partially, or completely, compromises treatment adherence and therapeutic alliance [11,12]. However, this can be avoided by integrating the guidelines with psychosocial consensus statements, in order to ensure more personalised treatment.

On the other hand, the BPSM also has some limitations in clinical practice: developing an in-depth relationship with a patient often requires more time and resources than are available, and physicians may prefer to rely on a bio-medical model that is more in line with their academic culture and training. Although they may theoretically agree with the BPSM. they are not always prepared to put it into practice.

The BPSM also has a number of other limitations [13]:

- holism is not always an advantage because some diseases have a specific pathogenesis and are sufficiently explained by a restricted causal model, and some medical treatments can offer sufficient, even if partial, solutions, such as antibiotics, antipyretics, and various surgical interventions;
- the BPSM may be difficult for clinicians, patients, and caregivers to apply in all of its biological, psychological and social aspects because of time and resource constraints, or a tendency to give more weight one aspect, rather than another, on the basis of personal preferences, qualifications or expectations;
- integrated treatments are always more effective than individual treatments alone, but sometimes one method may be more viable.

In his paper "*The rise and fall of the biopsychosocial model*" (2009), Nassir Ghaemi said that the BPSM was initially valuable as a reaction to biomedical reductionism but has played out its historical role [8]; or it may be more advantageous to apply one model or the other depending on the conditions. As Osler said in 1932,

"*Medicine is an art based on science, not simply a science, but also not merely an art*" [14], and other authors agree [15].

The current concept of disease

Combining the biomedical model and BPSM offers an opportunity for dialogue between the psyche-soma dichotomy and psychosomatics. Biopsychosocial factors may facilitate, sustain, or modify the course of a disease, and their relative weights may vary from disease to disease, from one person to another and, sometimes, from one time to another in the same person [8]. Furthermore, no single disease, patient or condition can be reduced to simply one characterising aspect, as all the determinants are always equally relevant in all cases. At the same time, at any given moment, the reference culture and the limitations and possibilities of circumstances may give more weight to one of the bio, psycho or social elements, thus leading to a preference for the disease over the illness framework or *vice versa*; and, in some optimal cases, they may be integrated with one another in order to promote a shared understanding and complementary decision making.

Nevertheless, some open questions remain: is it still appropriate to acknowledge the psyche-soma dichotomy, and can we still consider psycho-social aspects non-biological? The neurosciences have recently reduced the gap between the psyche and the soma, as a result of the development of epigenetics, psycho-neuro-endocrine immunology, neuroimaging, and other approaches, and this raises the question as to whether we are approaching the Rosetta Stone of psychosomatics.

The psyche-soma relationship is being replaced by the co-pathogenetic hypothesis.

Over the last few years, our view of the relationship between the psyche and the soma has developed from traditional concepts of inter-connection, influence (indirect activity and co-morbidity to the newer concepts of overlapping, causality

(direct activity) and co-pathogenesis. It is now known that various psychic and somatic alterations share the same biological mechanisms, and have common physiological patterns and pathogeneses: for example, it is widely acknowledged that mood alterations are very frequently associated with pain [16], but this relationship cannot be fully explained by simple co-morbidity, as depression and pain share important pathogenic mechanisms [17-20] involving a series of factors:

- **Neurotransmitters.** A reduction in the levels of serotonin (5HT) and norepinephrine (NE) in limbic areas not only induces a depressed mood, but also and simultaneously reduces the descendent inhibitory system and thus promotes an increase in pain; furthermore, dual anti-depressants (e.g., duloxetine, milnacipran, venlafaxine) act effectively on both depression and pain.

- **Hypotalamus-pituitary-adrenocortical (HPA) axis hyperactivity.** Depression can manifest itself under conditions of chronic stress, characterised by HPA axis hyperactivity. The functioning of the HPA axis is influenced by a subject's cognitive evaluation of, and emotional response to the stressor, which is why cognitive behavioural therapy (CBT) can reduce chronic stress. Nevertheless, the cascade of stress hormones, released upon HPA activation, increases the production of pro-inflammatory cytokines, and leads to the exacerbation of pain and a depressed mood.

- **Cytokines** play a dual role in the physical and emotional aspects of pain and mood: the increase in pro-inflammatory cytokines associated with diseases, such as cancer, causes pain and psycho-behavioural symptoms such as fatigue, depressed mood, and cognitive impairment [21-23]. These symptoms are related to each other by neurotoxicity: the central nervous system (CNS) reacts to a stressor by activating microglia, which increases the production of inflammatory mediators (cytokines), and astrocytes, which increases the glutamate release causing neurotoxicity. Confirmation of the complex relationship between the psychological (mood) and

somatic property (pain) of cytokines is provided by the immunological hypothesis of suicide during the use of interferon to treat multiple sclerosis [24-26], and the cytokine storm associated with COVID-19 [27]; furthermore, the involvement of inflammation in the etiopathogenesis of depression is suggested by the fact that patients with major depressive disorder and increased levels of pro-inflammatory cytokines (mainly IL-6, TNF-α and IL-1β) may benefit from anti-inflammatory treatment [28].

- E**xcitotoxicity**: The persistent excitotoxicity associated with chronic stress leads to neuronal sufferance and death with parenchymal hypotrophy, as confirmed by the neuroimaging of hippocampal shrinkage [29], the biological substrate of depression and pain. Anti-depressants can counteract this process by favouring the production of neurotrophic factors.

- **Allopregnanolone** is a neuro-hormone that inhibits glutamatergic neurotransmission by negatively modulating N-methyl-D-aspartate receptors (NMDAR) function and potentiates GABAergic activity, thus acting on both depression and pain. Anti-depressants also act on mood and pain by favouring the synthesis of allopregnanolone [30,31].

- The **microbiota** involved in the pathophysiology of many intestinal and extra-intestinal diseases provide a further example of co-pathogenesis, as recent research has demonstrated that it regulates many of the physical and emotional aspects (mood, anxiety, stress) [32-34].

- **Oxytocin** is a paradigmatic example of dual (psychic and somatic) activity. It has long been known that its somatic activity strengthens uterine contractions and favours post-partum milk excretion, but more recent findings show that it also induces maternal behaviours, such as empathy, and potentiates social behaviours and bonding by increasing trust [35,36].

The biological effects of psychological interventions

It is well known that biological drugs such as anti-depressants, steroids, and immuno-modulators can induce emotional changes, but it is possibly less widely known that psychological interventions can induce a biological response, as a number of studies have shown that psychotherapy enhance cancer survival and improve emotional disorders such as depression, anxiety, and stress [37,38].

The effect of psychological interventions on the biological mechanisms of disease seems to be due to their capacity to induce neurobiological changes, such as increasing the immune activity of natural killer cells [39,40]. Studies have found that psychotherapy mediates the immune changes involved in survival [41] by down-regulating the expression of pro-inflammatory genes and up-regulated type I interferon response genes in circulating leukocytes [40,41]. Shields *et al*. (2020) have also recently shown that psychosocial interventions (especially CBT) are associated with positive changes in immunity over time, including an increase in beneficial and decrease in harmful immune functions [43].

The biological activity of psychotherapies is also reflected in the brain changes induced by anti-pain treatments. A number of recent neuro-imaging studies have shown that psychological interventions such as CBT, meditation, mindfulness, and hypnosis can induce significant modifications in the brain areas and functions involved in modulating pain: for example, CBT favours a cortical control mechanism in patients with chronic pain by increasing the activation of the pre-frontal cortex (PFC), which is associated with executive cognitive control of pain. Moreover, the pain regulation induced by cognitive and meditative therapies can have a positive impact on nociceptive and non-nociceptive brain regions as it increases pre-frontal, orbito-frontal, somatosensory, anterior cingulate, and insula cortical activity, and decreases thalamus activation [44]. The effects of hypnosis on pain are mediated by the activity of the anterior cingulate cortex (ACC), the area involved in the "suffering" component of pain and unpleasant affective reactions [45-47]. Similarly,

other studies have shown that inhibition of afferent nociceptive transmission can be explained by a dramatically decreased activity of the thalamus observed under hypnotic induction, and the hypnotic mediation of executive, salience, and default networks [48,49]. Mindfulness can also provide pain relief by favouring orbito-frontal and rostral anterior cingulate cortical regulation of the thalamus and primary somatosensory cortex, and de-activating the posterior cingulate cortex. Prolonged mindfulness training is also associated with pre-frontal de-activation and greater activation of the somatosensory cortex, thus moderating the perception of painful sensations [50-52].

The psyche-soma overlap requires an integrated approach

Given all the evidence mentioned above, psycho-social, and somatic factors should both be considered in order to obtain a complete clinical response in a number of diseases, and these interventions should be implemented by means of a patient-centred, interdisciplinary therapeutic approach in order to ensure the greatest improvement in a patient's condition.

For example, the treatment of chronic pain should move away from analgesic therapy alone and towards multi-dimensional interventions, that include the use of different drugs and emotional, behavioural, and cognitive treatments. Treating chronic pain with analgesics alone is considered satisfactory by only about 40% of patients, because the psychosocial components of pain are under-evaluated and under-treated [18].

Another example is the co-morbidity of depression and a somatic pathology such as the menopause, rheumatological disease, diabetes, or thyroid disorders, to which a complete response can be obtained using drugs that are active on both, such as hormones and anti-inflammatory treatments, including monoclonal antibodies [55,56].

The impact of social factors on the soma

The socio-economic and relational components of the BPSM are integral parts of diagnosis and treatment. More than ten years ago, inspired by Kroenke *et al*. [57], Chida *et al*. [58], Pinquart *et al*. [59], Lutgendorf and Sood [60] pointed out that social adversities, such as isolation, considerably affect not only a patient's quality of life, but also disease progression, by modifying the cellular immune response, angiogenesis, invasion, anoikis, and inflammation [60].

Environmental factors, such as negative life events, socio-economic burdens, relationship difficulties, social isolation, and dysfunctional individual attitudes and coping strategies, stimulate the activation of the neuroendocrine response of the HPA axis, autonomic nervous system, catecholamines, glucocorticoids and other stress hormones and neuropeptides, and neuroendocrine stress hormones have a systemic effect on disease progression [60-67].

It is also known that emotional responses to psychosocial problems may be related to an increased chronic release of norepinephrine, as demonstrated by autonomic alterations under stress conditions.

Poor social support and distress can impair the immune activity of T cells, NK cells and neutrophils [64] and induce the up-regulation of 67 mesenchymal-characteristic gene transcripts and the downregulation of 63 epithelial-characteristic transcripts [65]. On the other hand, social support favours resilience against stress, has positive physiological and immune effects [66], and is related to less leukocyte pro-inflammatory and pro-metastatic gene expression [67].

The psyche and the soma in fibromyalgia

One clinical context that widely expresses the unity of the pathogenetic, clinical and therapeutic aspects of psychosomatics is the fibromyalgia syndrome (FM), about which there is still debate as to whether it should be defined as an illness or a disease. FM is characterised by the simultaneous presence of physical symptoms (pain,

irritable bowel syndrome, headache, etc.), psychological disorders (depressed mood, anxiety, insomnia, alexithymia, etc.), and psychophysical symptoms (fatigue, cognitive disorders, etc.) [68], which may not only vary from patient to patient, but also within the same patient during its course. This greatly increases diagnostic difficulties because, on

the basis of the concepts discussed above, these symptom clusters cannot just be considered co-morbidities, but need to be interpreted in terms of their co-pathogenesis [69-70]. FM has been called a *chronic central sensitisation syndrome*, a condition that leads to alterations in a person's sensitivity to pain. It is clinically characterised by allodynia (pain in the absence of painful stimulation) and hyperalgesia (increased pain upon painful stimulation); neuro-physiologically characterised by reduced pain thresholds and prolonged electrophysiological responses; and psychologically characterised by the unpleasant quality of the perceived pain, a broadening of the pain attentive field, and catastrophism [71].

Early studies of FM concentrated on its *stress-related origin* [72-73] but, although the idea of stress and trauma is still very important [74], it is now clear that its pathogenesis is due to many different biopsychosocial factors such as genetic neuroendocrine, socio-cultural and, perhaps, even biohumoral factors [75-76]. This is confirmed by the fact that the symptoms of FM can be alleviated by treatments that modulate inflammation [77], and that anti-depressants are a useful means of decreasing the perception of pain even in non-depressed patients [78].

The origin of chronic widespread pain is very complex, and FM is a condition that allows us to reflect on some very important concepts, above all whether the location of the pain is in the brain (psyche) or the body (soma) (Fig. 1). In most patients, neuro-psycho-pharmacological treatments alone are unsatisfactory in controlling pain, and only an approach that covers all the pathogenic components of the syndrome leads a substantial improvement in symptoms. This underlines the

centrality of the psychic dimension in the pathogenesis and treatment of FM pain and confirms the pathogenic unity of the psyche and the soma.

From this point of view, within the last few years, has been emphasized, in the treatment of fibromyalgia, a patient self-management approach: the unsatisfactory result of a single therapeutic intervention advises the integration of multiple types of care (analgesics, psychodrugs, psychotherapies, physical exercise, relaxation techniques, physical care, etc.). Of paramount relevance, in this management, is that the patient should be pro-active, through a psycho-educational approach and a close monitoring of its adherence to treatments [79].

Conclusions and improvement proposals

Further evidence supporting the theoretical and neuroscientific basis of psychosomatics will improve our understanding of the way in which the mind and body share the same pathological pathways and curative strategies. It is also important to give more consideration to the interconnectedness and overlapping of the psyche and the soma in clinical practice: psychosomatics may be an old concept, but its clinical application is still hampered by cultural and economic resistances.

The psychosomatic spectrum of therapeutic strategies needs to be broadened: diseases should also be confronted as illnesses requiring consideration all their biopsychosocial features in a patient-centred manner in order to avoid therapeutic failures due to partially effective or ineffective interventions (Fig. 2).

To convert this perspective to clinical practice, more economical, human, spatial and temporal resources should be invested to create new opportunities, services, and care pathways. A holistic approach necessary require the effective realization of interdisciplinarity, with various healthcare professionals working in an integrated and aligned way with the same patient.

This gap between theory and practice could depend both on the choices of the sanitarian institutions, services, and structures and on the individual healthcare

provider's sensitivity, attention, awareness, and training on these aspects. In fact, the individual attitudes can play a role in favouring or hindering the integrated care. Training and education in psychosomatics should be improved: at the academical level more interaction between different university departments, more interdisciplinary formative occasions, and more contamination of other subjects in the teachings (e.g., delivering courses of psychology to medical students or of medicine to psychology students or deepening of a theme of common interest by several teachers with different professional profiles) could be useful; during work, interdisciplinary refresher courses or greater information exchange (national and international) between teams, centres or nations could provide suggestions for new ways of applying the care models.

Finally, care attention should be always share between the patient and the healthcare provider: healthcare professional's personal difficulties, poor attitude to adequate communication, psychological concerns, personological traits, or work-related distress could negatively impact on his/her attitude towards the patient, creating distances from the ideal care. Thus, promoting and guaranteeing interventions and spaces of self-care for the healthcare providers is a preventive and protective action that could contribute in exceed the application limits of the BPSM.

The BPSM should become an integral part of clinical practice whenever a psycho-social component can be assumed. The Hippocratic aim "*to cure sometimes, to heal often, to console always*" has all of the strengths and none of the weaknesses of the BPSM. The time and resources required may well increase but, in the long run, the clinical and human advantages gained will certainly justify the initial investment in terms of the quality and costs of care.

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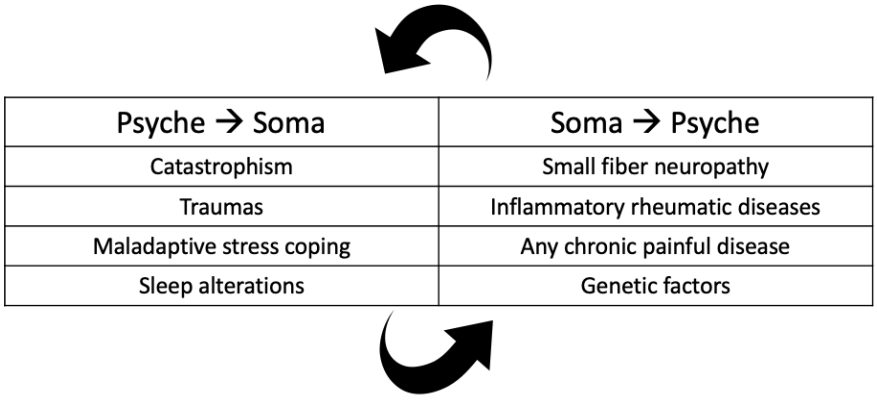
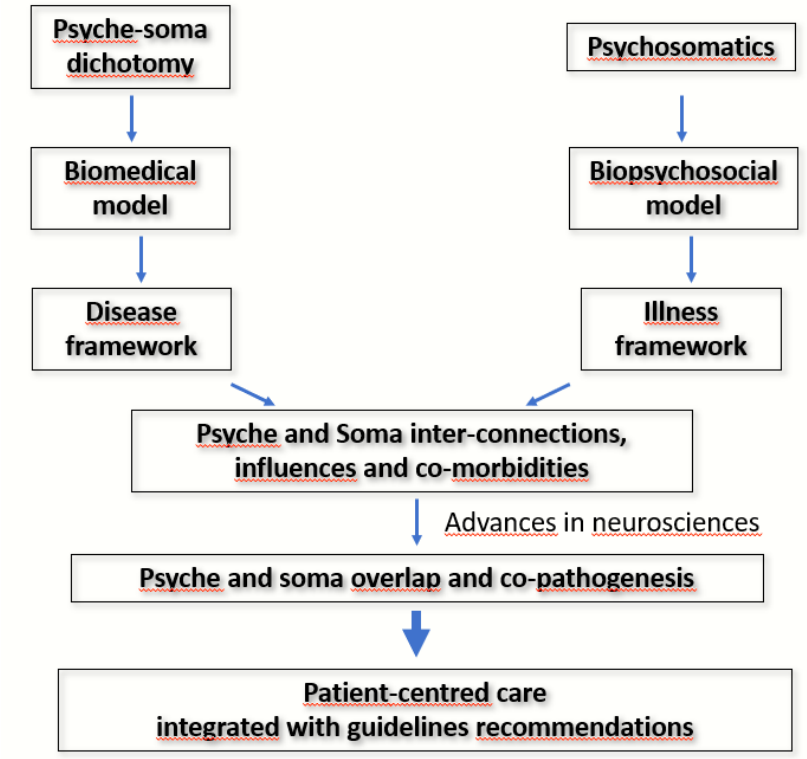
FIGURES

Figure 1. The etiopathogenetic conundrum of fibromyalgia syndrome: reciprocal influences and common psyche-soma pathways.



Psyche → Soma	Soma → Psyche
Catastrophism	Small fiber neuropathy
Traumas	Inflammatory rheumatic diseases
Maladaptive stress coping	Any chronic painful disease
Sleep alterations	Genetic factors

Figure 2. Psyche-soma dichotomy or psychosomatics: which is more clinically appropriate?



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