Società Italiana di Psichiatria

Evidence based Psychiatric Care
Journal of the Italian Society of Psychiatry

Giovanni Biggio

Therapeutic efficacy and tolerability of phospholipid liposomes (Liposom Forte®) for the management of depressive disorders in elderly patients

Giovanni Biggio[1,2], Maria Cristina Mostallino[2], Francesca Biggio[1], Antonino Minervino[3], Francesca Giannetti[4]

[1] Department of Life and Environmental Sciences, Neuroscience and Anthropology section, University of Cagliari, Monserrato (CA), Italy; [2] Institute of Neuroscience, National Research Council, (CNR), Italy; [3] Chairman Italian Society of Psychosomatic Medicine (SIMP), Scientific Director of the Italian Higher Institute for the Fight against Stigma (ASILS); [4] Hospital Psychiatrist, UOP 25, ASST-Cremona Local Health Authority

Abstract

Depressive disorder in elderly patients is a particularly important and complex clinical condition. For many people, the likelihood of experiencing a depressive disorder is very high after the age of 65. This probability increases if they have a history of mood disorders, if their health is impaired for other reasons, if they have unfavourable social and environmental circumstances, and, in other words, if they present all the characteristic "frailties" of the elderly. In addition to and alongside psychotherapy, the role of antidepressants such as SSRIs, SNRIs and NaSSAs remains key as first-choice half-dose therapy. Aspects to be taken into consideration include possible interactions with ongoing treatments, greater susceptibility to side effects and their intensity, and, lastly, the duration of the latency period, which is more or less twice that shown in adult patients, which could therefore lead to reduced compliance. For all these reasons and on the basis of the data emerging from experimental models and clinical research on the role of phospholipid liposomes (PL), it would appear clinically useful to include PLs as an add-on to antidepressant treatment plans. In the last two decades, the availability of a molecular super technology has highlighted both the crucial role played by membrane phospholipids in ensuring optimal neuronal function in the adult brain and the relative loss of their efficacy during the ageing process. Indeed, the ageing of the brain is linked to a progressively rapid involution of neurons both functionally and structurally. In the elderly, this often translates into a reduced capacity for adapting to physical, social and environmental conditions that are not perfectly suited to them, which makes them more fragile and vulnerable to mood disorders. Given that the efficacy of membrane phospholipids in ensuring the function and plastic properties of neurons diminishes physiologically as part of the ageing process, with a consequent increase in sensitivity to stress, this paper proposes a treatment with PL in depressive and anxiety-depressive disorders in the elderly. The sophisticated and important data emerging in experimental neurobiology, neurochemistry and super microscopy demonstrate the effectiveness of treatment with PL in preventing or antagonising the functional and morphological changes caused by chronic stress in the brains of rats. These experimental data are a solid neurobiological basis for the clinical studies referenced in this paper on the effectiveness of PL administered as monotherapy or as an add-on to antidepressant therapy.

Key words: ageing, neuronal plasticity, depression, late life, phospholipid liposomes (PL), liposomes, phospholipids

How to cite this article: Biggio G, Mostallino MC, Biggio F, et al. Therapeutic efficacy and tolerability of phospholipid liposomes (Liposom Forte®) for the management of depressive disorders in elderly patients. Evidence-based Psychiatric Care 2020;6:76-91. https://doi.org/10.36180/2421-4469-2020-13

Correspondence:
Giovanni Biggio
giovanni.biggio@libero.it

Conflict of interest
Giovanni Biggio declares no conflict of interest.

Introduction

Mood is an essential component of existence. It is attuned to the natural ups and downs of life, fluctuating according to the actual perceived quality of what is experienced during the course of existence, staying balanced or tilting towards melancholy, sadness, joy, cheerfulness or euphoria. This modulation is needed for the proper perception of subjectivity, which helps individuals learn from experience and be in relationship with their internal and external contexts.

If accentuated and persistent, mood variations are a pathological condition that has nothing of the adaptive value of natural fluctuations. Instead, it is a form of suffering with the potential to seriously alter the course of an individual's life. In this sense, mood can deviate as far as depression, or expand to include mania or, as in the case of bipolar disorder, can involve varying combinations of these two extremes.

Depression is a relatively widespread disorder, which tends to become chronic and is often comorbid with other psychiatric and/or somatic disorders. It is twice as likely to affect women. The incidence at six months ranges between 1% and 3%, whereas the lifetime incidence is 15%. No age group is spared, although the highest rates are seen in adults.

The therapies for depression recommended by the most authoritative international guidelines and confirmed in clinical practice focus on the use of antidepressants, psychotherapy and combination therapy. It remains uncertain whether the use of antidepressants is appropriate in mild forms, whereas it is certainly beneficial in moderate forms and indispensable in severe forms. Combination therapy – drug therapy and psychotherapy – is certainly preferable in terms of better and proven results. Worth noting is the latency period for antidepressants, that is, the time needed for an appreciable therapeutic action of the drugs. This is a delicate period in the management of patients, who may have to tolerate side effects, which are even more evident in elderly patients, before being comforted by the therapeutic benefits. Moreover, while this latency is estimated at around two weeks for adult patients, in elderly patients with depression it is considerably longer [1].

Late-life depression deserves, for reasons we will discuss, its own position in the wider context of the diagnosis of depression.

In recent decades, numerous epidemiological studies on depression, universally highlighting an increase in depression rates in over 60-year-olds, have underlined the need to consider the elderly as a subgroup at greater risk of developing depression and with specific clinical characteristics and therapeutic issues [2].

In the over-65 age group, the incidence of the various clinical forms of depression ranges from 9% to 24% in different European countries, averaging 12% [3]. Forecasts for Italy point to 33% of the population being aged over 65 by 2065, with a consequent increase in age-associated diseases, including, naturally, depression [4].

A proper representation of the epidemiological dimensions should take account of the significant consensus in the literature that this phenomenon is underestimated. This is in part because the clinical presentation of depressive disorders may involve a broad spectrum of somatic manifestations (masked depression), but also because some presentations are subthreshold and therefore, by their very nature, are more easily overlooked in diagnosis [5,6].

Prevalence is much higher in residential healthcare facilities [7] and, as with all clinical presentations of mood disorders, the female population is more affected. Impaired mood in advanced age exacerbates the fragility of the elderly, increasing disability and the risk of suicide [8].

Fragility in the elderly reflects a series of age-related physical and pathological changes affecting multiple systems, which makes this population more vulnerable [9].

For initial diagnostic guidance, it is essential to consult the most common diagnostic manuals, such as the DSM-5 or the ICD-10. In the DSM-5, diagnoses include major depressive disorder (MDD), dysthymia, substance/medication-induced depressive disorder and depressive disorder due to another medical condition. All these possible diagnoses have specific aspects and clinical manifestations that can make these diagnostic systems too rigid and too narrow to be used with the elderly.

MDD accounts for 3.3% of cases in the over-65 age group, but rises to 27% in the over-85 age group, and a diagnosis of depression at an earlier stage of life acts as a predisposing factor [9].

Polypathology is involved in more than 80% of cases, especially where there are cardiovascular, bone and joint, and respiratory diseases, pain syndromes, cancers and metabolic disorders. The rate of comorbidity with one or two illnesses is lower. Comorbidity is also higher with neurological syndromes such as Parkinson's disease and epilepsy, insomnia and neurodegenerative diseases. This leads to a significant reduction in quality of life, as well as an increase in mortality and suicide [10].

Masked depression and subthreshold depression are the other two most frequent diagnostic categories (5% and 11% respectively) [6,11,12].

Within the natural evolution of the cycle of life, ageing involves changes within individuals, their social context and the quality of their life experiences. Quality of life in the elderly depends considerably on a series of existential events that may be more or less favourable, the resourcefulness of the context and, more generally, the extent to which ageing is stigmatised within a given culture.

The onset of illnesses associated with this age group has a significant impact on quality of life, especially when those affected have no family or social resources.

Depression becomes part of this complex picture of frailty, both as an independent factor and as a consequence. It

has a heavy impact on what is often an already impaired quality of life, worsening the prognosis of concomitant illnesses, unleashing a vicious cycle that often spirals drastically to reduce life expectancy or leads to suicide.
It is therefore a significant problem in terms of the number of people affected by or at risk of developing depression in advanced age, owing to the difficulty recognising it and treating it appropriately.

Pathophysiology of depression

Neurotransmitters and receptors

Recent studies on the neurobiology of depression suggest that the most important neurochemical and molecular events involved in the modulation of the emotional and affective states include significant modifications in gene expression and, consequently, in the density, sensitivity to stress stimuli and function of the receptors of some of the most important neurotransmitters, such as serotonin, noradrenaline, dopamine and GABA [13,14]. Specifically, the functional changes of these receptors in response to their activation by the respective neurotransmitters play a crucial role in controlling the mechanisms of adaptation to both acute and chronic stress stimuli. The functional potentiation or decrement of these mechanisms in specific areas of the brain translates into a substantial reduction or increase in resilience mechanisms as well as in the perception of stress stimuli. In particular, noradrenaline and serotonin are thought to be the two key neurotransmitters, in terms of aetiopathogenesis and neuropsychopharmacology, for the control and modulation of mood. Serotonin plays a crucial role in the control of emotions and is significantly involved in levels of aggressiveness, suicidal behaviour and violent behaviour. Noradrenaline, particularly through its prefrontal action, plays a role that is equal in importance to dopamine in the control of cognitive functions, by modulating decision-making capacity and, more in general, executive functions.

Hypothalamic-pituitary-adrenal axis

The hypothalamic-pituitary-adrenal axis (HPA) plays a crucial role in amplifying or reducing the capacity for adaptation to stress stimuli. Therefore, long-term alterations in the secretion of cortisol are generally associated with the pathophysiology of depression and, more in general, with the cognitive disorders associated with this pathology.
In physiological conditions, the cortisol released acutely by the adrenal glands is crucial for activating, especially in the prefrontal cortex, the neurons responsible for modulating executive functions. Conversely, depressive disorders are associated with dysregulation of the function of the HPA axis and the consequent changes in cortisol secretion [15]. Patients with severe depression often have persistently high levels of cortisol as a consequence of an elevated activity in the axis or, conversely, a significant reduction in the secretion of this hormone [16-19]. Both pathological conditions are associated with a reduction in neuronal plasticity, a neurochemical process that leads to reduced cognitive, affective and emotional performance, which may differ in terms of intensity and quality according to the depressed subject [20].

Depression and neuroplasticity

Evidence that the morphology of neurons changes in different physiological and pathological conditions shows that the adaptation of these cells to environmental stimuli mainly occurs through morphological changes.
The demonstration that chronic stress leads to a loss in neuronal plasticity – that is, a reduction in adaptation mechanisms to both acute and chronic stress, an effect that is partially reversed by antidepressants and environmental and social enrichment – suggests that depressive disorders could be linked to progressive neuronal atrophy and the consequent inability of neurons to adapt to negative environmental conditions [14,21]. This conclusion is supported by more recent studies, including modern super-resolution microscopy in experimental contexts and, in clinical settings, through brain imaging. This research has shown that the brain of animals subjected to repeated stress stimuli and those of untreated depressed individuals often present significant neuronal atrophy (animals) [14,21] and a reduction in the volume of specific areas (hippocampus, cortex) of the brain (humans) [22] involved in affective and cognitive regulation.
Overall, these studies suggest that the plastic properties of neurons are a potential and crucial natural resource in which it is possible to intervene to improve sensitivity and resilience to stress and, consequently, adherence to and the efficacy of treatments in depressed individuals. These conclusions are strongly supported by studies on the functional and structural changes of the brain caused by social interactions [23] including those taking place online.

The neuroplastic brain

Humans have the most evolved brain among mammals. The development of areas of the cortex has enabled humankind to develop the outstanding cognitive functions that represent “man’s privilege” over other species living beings on the planet.
The extraordinary morphological and functional remodelling of synapses seems to depend on equally extraordinary variations in gene expression. Indeed, it is thanks to this property that genes continually change the morphology and function of our neurons in response to environmental input and life experiences. Thus, conditions such as vulnerability and resilience depend on rapid and long-lasting changes in our gene function, which go hand in hand with functional and structural changes to neurons and, more generally, brain plasticity.

Evidence suggests that the gene should not only be considered an entity whose fairly rigid structure changes with evolution and transmits our traits from one generation to the next, but also an extremely dynamic entity that is capable of radically modifying its function in response to environmental stimuli (social environment, cultural environment). This so-called "epigenetic" property can be defined as any phenotypic variation resulting from a functional alteration of the gene, rather than being attributable to a variation in the structure of the same gene. Epigenetic changes are due to extremely dynamic chemical mechanisms through which a "structurally rigid genome" can respond functionally and extremely rapidly and dynamically to various and multiple environmental changes. This translates into the expression of different phenotypes from a single genome (monozygotic twins). Brain imaging techniques strongly support this fundamental concept of modern neuroscience.

Thanks to its adaptation and plastic properties, the brain changes constantly throughout the course of life. Thus, emotions, socialisation, socio-economic status, trauma, chronic stress and diet are all factors that constantly change the plasticity of the brain and the connections between neurons. Epigenetic mechanisms have therefore determined and continue to shape the evolutionary history of our brains [24].

The clinical impact of depression in the elderly

The manifestations of depression in the elderly can be unusual enough to justify use of the term "atypical" and this can make it difficult to identify, diagnose and treat appropriately.

When determining onset, genetic predisposition generally plays a lesser role than psychosocial events, comorbidity and the normal ageing process of the brain. Moreover, the clinical signs of late-age onset depression are often evaluated as normal manifestations of life for that age group.

Depressed mood, loss of interest and pleasure, poorer relationships, lack of energy and insomnia, and anxiety (60-90%) comorbid with more severe depression [25], somatisation [26], hypochondria and suicidal ideation, blunted affect, apathy [27] and impaired function are clinical aspects that are specific to depression with onset in later life.

When the clinical manifestations are more vague and lie "subthreshold", it is more difficult to recognise, despite the high level of disability that it causes [2].

Depression with onset after 50 years of age is often defined as late-onset depression (LOD) and is characterised clinically by apathy, neuropsychological deficit and psychomotor retardation [28-30]. In elderly subjects with depression it is common to see mild cognitive deficit and psychomotor retardation where these are not part of dementia and are attributable to a brain state affected by vascular and neurodegenerative factors. These symptoms improve if the depressive disorder is treated appropriately, although they do not lose their predictive value for an evolution towards dementia.

Delusional or hallucinatory components of psychosis are not rare, and often involve ideas of ruination and catastrophe, hypochondria or persecution [31].

There is often comorbidity with various somatic conditions, particularly the metabolic, cardiovascular and oncological disorders that commonly arise in later life, and with neurological and neurodegenerative disorders whose symptoms can mask a depressive state (masked depression) or switch off the patients affective condition (depression without sadness) [32,33].

Another important aspect to take into consideration in elderly patients is mood alterations resulting from neuroendocrine disorders. Partial androgen deficiency of ageing males (PADAM) should be considered for men with MDD. This manifests as a variety of behavioural symptoms such as weakness and fatigue, depressed mood, lack of motivation, decreased performance at work and in sport, decreased vitality, increased anxiety and irritability, insomnia, difficulty concentrating and impaired memory [34].

Clinical studies have highlighted a greater variation in mood by up to 23% in pre- and post-menopausal women. Furthermore, symptoms of anxiety, tension, nervousness, panic and preoccupation are reported more frequently during pre-menopause, irrespective of the presence of symptoms of depression [35].

The neuroendocrine and neurotransmitter changes observed during menopause are the pathophysiological conditions behind the mood disorders and the alterations in cognitive function seen during this period. Post-menopausal changes in neuropeptides and neurotransmitters are involved in the pathogenesis of the mood disorders characteristic of this phase of life. In particular, noradrenaline, serotonin, opioid peptides and neurosteroids appear to be involved [36].

Lastly, mention should be made of "depressive pseudodementia", another form of depression in the elderly which manifests with cognitive symptoms, changes in attention, memory, concentration, disorientation, confusion and social withdrawal. What distinguishes it from dementia is its sudden onset, the rapid establishment of its clinical picture and, above all, the effectiveness of antidepressant therapy [37].

It is clear that it is important to intercept, diagnose and determine appropriate treatments for depression in elderly individuals. Certainly, the clinical complexity of elderly patients makes it all the more difficult, because the tendency is to deal first and often only with the somatic illness, because the symptoms of depression are misread and considered "normal" aspects of the life of the elderly, because there is no support in their social context and dignity is not given to certain types of suffering, and because the right to treatment is not so clear-cut [38].

It is equally evident that the health of an elderly person is at serious risk of severe and irreversible impairment if

negative social and environmental conditions and symptoms related to the affective sphere, particularly depression, are not identified and managed [39].
Comorbidity with medical and/or neurological disorders makes the diagnosis of depression more difficult, because they are more evident. Yet, such illnesses are negatively affected by a failure to diagnose and treat the depressive order, which worsens their prognosis, increases the risk of mortality [40], disability resulting from extended hospital stays, institutionalisation and related direct and indirect costs [41,42].
Thus, both diagnosis and treatment may be delayed, in a vicious cycle where one element affects the other. Somatic symptoms prevailing over affective symptoms, an atypical clinical presentation of depression, the interdependence of somatic factors and psychological factors, and the importance of psychosocial factors all make depression in the elderly an important, complex and often ignored and underestimated clinical issue.
From this we can deduce the importance of the therapeutic approach, although this, too, has its complexities.
Often what prevails is the importance of medical therapy, despite the fact that treating the depression has a positive effect on the medical condition itself and improves its prognosis [2].
On the other hand, the very existence of the depressive disorder negatively impacts treatment compliance and lifestyle [43]. The condition of elderly subjects, especially when marked by illness, increases their sensitivity to the side effects of antidepressant therapies and to their neurotoxicity when there are concomitant neurovascular or neurodegenerative disorders. Furthermore, comorbidity itself, which is very frequent, entails multiple therapies which increase the risk of side effects, drug interactions and toxicity in patients who are by nature fragile and vulnerable [1].
This is why treatment adherence is seriously jeopardised, but poses a challenge for healthcare workers to be aware of the value and importance of managing elderly depressed patients, by enhancing their knowledge of this particular widespread clinical issue, and by increasing their own relational skills [44].

Phospholipid liposomes as therapeutic agents

Membrane lipids play an important role in regulating neuronal function in the brain [45]. The brain's lipid composition can vary according to individual regions, specific subtypes of neurons and even in certain cellular subcompartments, significantly affecting neuronal activity and, consequently, the threshold and cellular sensitivity to environmental stimuli and, therefore, subjective perception and emotional states.
Most lipids are located in the plasma membrane. Their main function is to form a barrier between the intra-and extracellular compartments, but they can also determine the location and function of proteins within the membrane in order to regulate the synaptic activity of neurons. Lipids can regulate exocytosis processes, and therefore the release of neurotransmitters, and also endocytosis processes, through a different role of second messengers inside neurons [46].
The lipid fraction of membranes in mammals is made up primarily of varying proportions of glycerophospholipids, sphingolipids and cholesterol. The proportions of these lipids differ in the various subtypes of neurons [47,48]. Phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol are some of the main glycerophospholipids contained in the membranes of mammals. These glycerophospholipids can in turn be transformed into different derivatives through the action of various phospholipases, and can thus be converted into phosphatidic acid (PA), and dyacylglycerol (DGA), which can perform different functions through their links with specific receptors.
The brain's lipid composition can be modified through diet and drugs containing combinations of these phospholipids, with direct consequences on mood and behaviour.
Several studies conducted in animals have shown that, in addition to causing overweight and obesity, fat-rich diets also reduce anxiety and locomotor activity, as well as increasing social interactions and aggressiveness, and decreasing the pain threshold [48-51]. These results show that the right changes in the availability of membrane phospholipids in the brain can control affect and emotions, with the related impact differing according to age and sex [49,52].
Environmental factors like traumatic events or chronic stress, which interfere with lipid synthesis [53,54], are often associated with changes in affect and the emotional sphere. One of the most current hypotheses on the biological mechanisms behind anxiety and mood disorders suggests that dysfunction in the mechanisms linked to the regulation of neuronal homeostasis [55] and, more generally, neuronal plasticity represents a greater vulnerability to the above disorder. Membrane lipids play a primary role in the control of all of these processes and, consequently, variations in their composition can affect the mechanisms of neuronal plasticity and therefore behaviours associated with anxiety and depression. A reduction in these phospholipids has been linked to a reduction in D2 receptors and dopamine, serotonin and noradrenaline receptors, as well as the enzymes involved in the metabolism of these monoamines, in several areas of the brain, such as the prefrontal cortex, the striatum and other areas that control emotions. Lastly, a reduction in phospholipids is also related to reduced levels of neurotrophic factors such as the BDNF (brain-derived neurotrophic factor) protein and reduced neurogenesis in the hippocampus, and increased interleukins, molecules that can inhibit stem cell differentiation in neurons [56].
As highlighted earlier, changes in neurotransmitter levels, in the activity of signal transduction systems and in the expression of specific genes are behind molecular

and neurochemical mechanisms that allow neurons to adapt morphologically and functionally to the various environmental, endocrine, pharmacological, and acute and/or chronic stress stimuli. Specifically, the mechanisms of neuronal plasticity are associated with morphological changes (changes in the arborisation and number of dendritic spines) and an increase in neurogenesis; phenomena linked to cognitive functions, learning and memory.

Recent experimental research has demonstrated that chronic stress causes neuronal atrophy with a reduction in the density of the dendritic spines and in the complexity of dendritic arborisation. It is also responsible for changes associated with reduced expression of neurotrophic factors and neurogenesis (differentiation and proliferation of new neurons) in the hippocampus, which is particularly evident during the ageing process of the brain with consequent cognitive, emotional and affective fragility.

In this paper, we report morphological and neurochemical data obtained in rats subjected to chronic stress preceded or followed by treatment for 4 weeks with PL, Liposom® Forte (LF).

LF is a mixture of neuro-homologous, hypothalamic phospholipids, aggregated into nanometric PL (< 200 nm), where the main components are phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine, which together represent approximately 90% of total phospholipids. Of these, phosphatidylserine appears to be the compound whose action is prevalent in the CNS [57]. The composition is characterised by a series of long-chain fatty acids that are unique in their effects on the CNS, in which C22:6 or docosahexanoic acid (DHA) is the most representative.

Parenteral administration of LF can penetrate the blood-brain barrier and stability studies have shown that these molecules remain stable in the blood and reach the brain intact. Administration of LF can: activate metabolism by

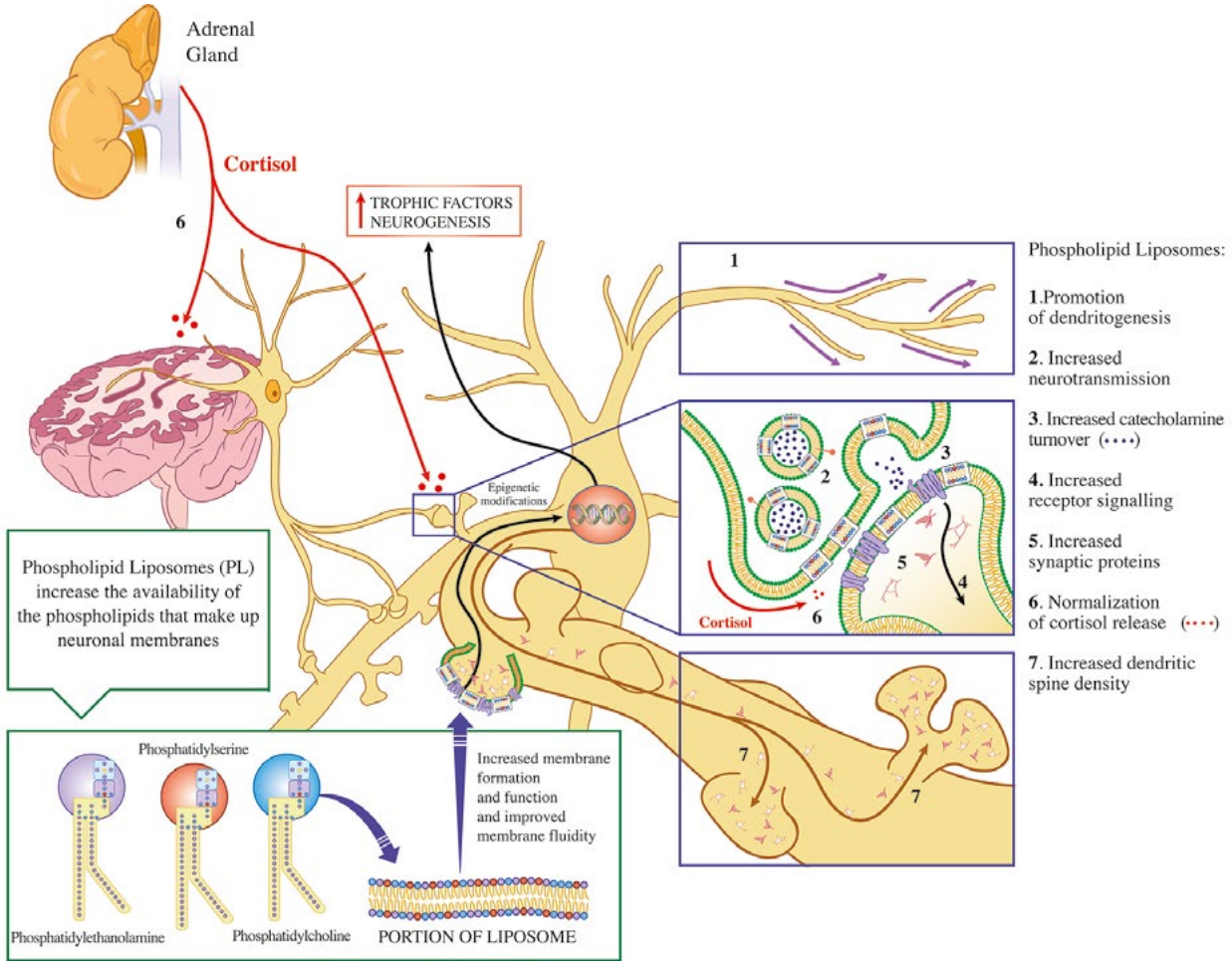


Figure 1.
The administration of PLs boosts the structure and improves the fluidity of neuronal membranes. This facilitates the molecular and functional link between the membranes and the nucleus through epigenetic mechanisms that can improve neurogenesis, the expression of trophic factors and synaptic plasticity.

the hypothalamus, increase serotonin and catecholamine (dopamine and noradrenaline) turnover; normalise cortisol secretion and reactivate neuronal plasticity. This pharmacological effect is particularly reflected in the function of the hypothalamic - pituitary - adrenal axis, thus indicating that this area can easily be reached by the drug. Lastly, it was observed in an experimental model that, by influencing the chemical and physical properties of neuronal membranes, hypothalamic phospholipids modify the receptor adaptation of central aminergic neurons to long-term antidepressant therapy [58,59] (Figs. 1, 2).
Therefore, supplying exogenous phospholipids can improve cellular activity in conditions of altered phospholipid metabolism and cell membrane function, such as physiological ageing or pathological processes like depression [60].

Study protocols

To test its efficacy in antagonising or preventing the negative effects of chronic stress on neuronal plasticity, LF was administered to rats belonging to different experimental groups. One group of animals was exposed to chronic stress for 5 weeks and, from week 1 of the start of stress, the animals were treated with LF for 4 weeks. The rats were exposed to unpredictable, chronic stress, receiving a new stressful stimulus every day [61]. To determine whether LF was capable of preventing the effects of stress, a second group of animals was pre-treated with LF (50 mg/kg, IP, for 4 weeks) and subsequently exposed to chronic, unpredictable stress for 3 weeks. The data obtained were compared with those from rats not subjected to stress and treated with a vehicle (Control group) or treated with LF (50 mg/kg, IP, for 4 weeks).
At the end of the treatment, the rats were killed and their blood was taken to determine plasma levels of corticosterone (CTS) and the brains examined: a) to study the density and morphology of the dendritic spines, the complexity of the dendritic arborisation using the Golgi silver staining method; b) to study cell proliferation and neurogenesis through BrdU (bromodeoxyuridine) immunolabelling (proliferation) or BrdU and the NeuN (neuronal nuclei) neuronal marker (neurogenesis).

Results

In line with a previous study [62], Figures 3 and 4 show that long-term treatment with LF is able to antagonise and

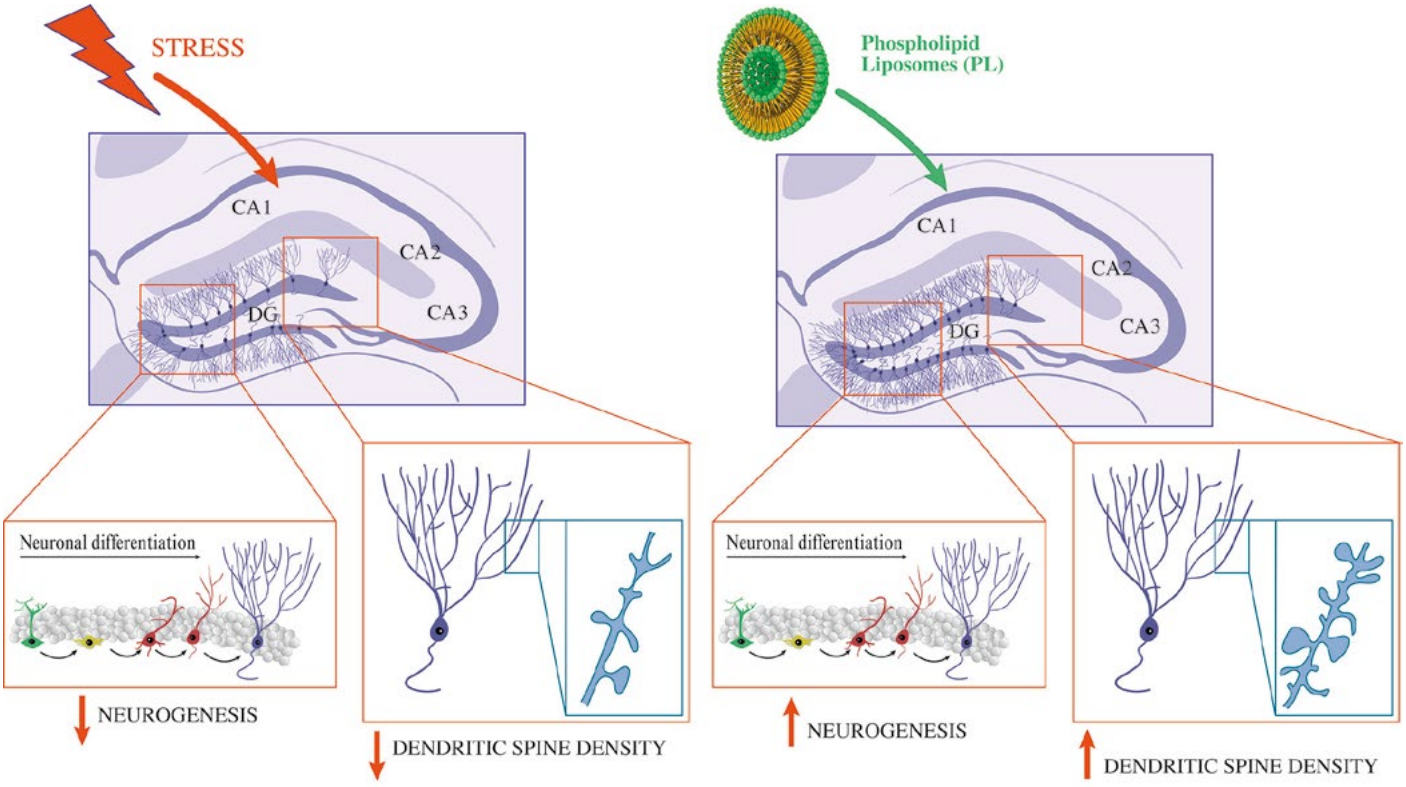
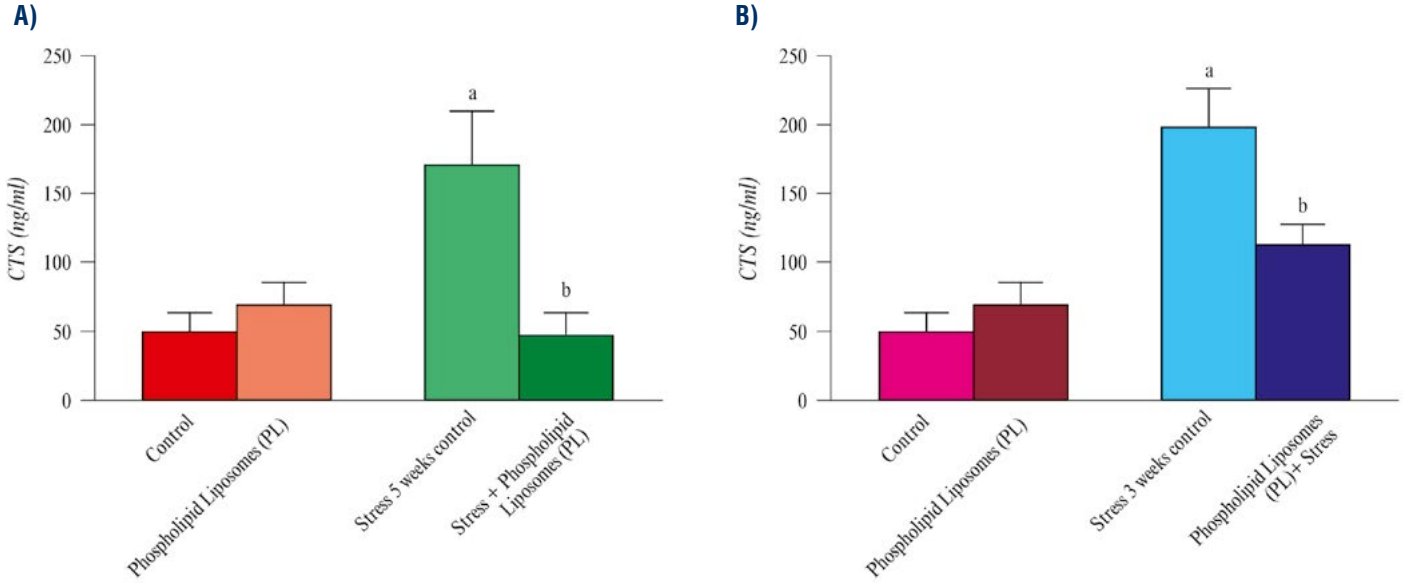


Figure 2.
Chronic stress reduces neurogenesis and dendritic spine density in the hippocampus of rats; this effect is antagonised by the administration of PL.

prevent both an increase in plasma CTS (Figs. 3A, B) induced by chronic stress and the inhibitor effect of stress on dendritic spine density (Figs. 4A-D) in the granule cells of the hippocampal dentate gyrus. In fact, 4-week pre-treatment with LF showed high efficacy in preventing a stress-induced reduction in dendritic spine density.
Treatment with LF over 4 weeks increases the density of stubby and thin spines in the granule cells of the hippocampal dentate gyrus (Figs. 5A, A1, B; C, C1, D), which, conversely, are reduced in the animals exposed to chronic stress for 3 or 5 weeks (Figs. 5A, A2, B; C, C2, D). Treatment with LF can antagonise (Figs. 5A, A3, B) and prevent (Figs. 5C, C3, D) the reduction in stubby and thin spines. Conversely, neither chronic stress nor treatment with LF modifies the density of mushroom spines (Figs. 5 A-D).
Chronic stress for 3 or 5 weeks reduces both cell proliferation (Figs. 6B, C) and neurogenesis (Figs. 7B, C) in the hippocampal dentate gyrus. Subsequent treatment with LF antagonises both the reduction in cell proliferation (Fig. 6B) and neurogenesis (Fig. 7B) bringing it back to the control values. Pre-treatment with LF prevents the reduction in both proliferation (Fig. 6C) and neurogenesis (Fig. 7C) induced by chronic stress.

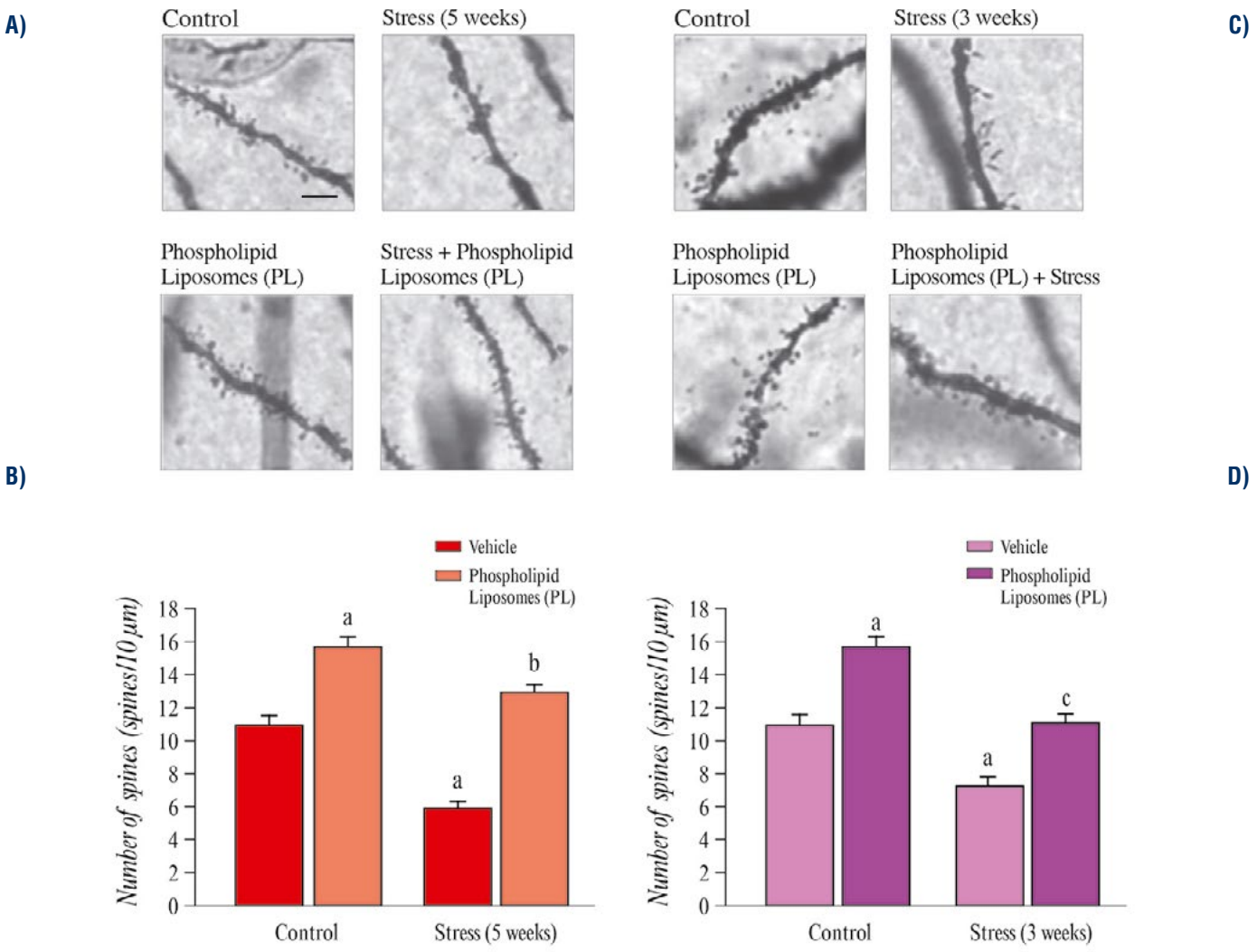
Clinical efficacy of phospholipid liposomes

Treating depression in the elderly patient presents a series of difficulties. First of these is choosing an antidepressant with the most appropriate balance between efficacy and safety, particularly as it will often be part of a polytherapy for the concomitant treatment of other clinical conditions, with a possible overlap in interactions and in the risks of side effects. Even more delicate is the issue of managing the classic latency in the action of antidepressants, given that the previously cited aspects already point to a risk of poor treatment adherence. Thus, it is necessary to seek strategies that might help control interactions between drugs and side effects and reduce the latency period in the antidepressant's action, enabling patients to stay motivated with regard to their treatment. Several data in the literature indicate that the latency period for elderly patients who have had previous episodes of MDD may be markedly longer than for younger patients (8-12 weeks *vs* 6-8) [1]. If there is no history of mood disorders, the delay in response is unlikely to be very lengthy [63], however the risk of relapse and recurrence remains very high in elderly depressed patients [64,65].
Antidepressants used in depression include selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs) like mirtazapine and more dated drug classes like tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) [66]. SSRIs, SNRIs and NaSSAs have become first-line treatments for most general practitioners, psychiatrists and other medi-



[a] P < 0.005 *vs* control; [b] P < 0.005 *vs* stress.

Figure 3.
Plasma levels of CTS in adult male rats subjected to long-term treatment with PL and/or stress for: **A)** 5; and **B)** 3 weeks. Long-term treatment with PL prevents the effects of chronic stress (3 and 5 weeks) on plasma levels of CTS. The data are expressed in ng/ml of plasma CTS and represent the mean ± SEM of 9-11 animals. The data are analysed using the two-way ANOVA test followed by the Newman-Keuls post-hoc test.

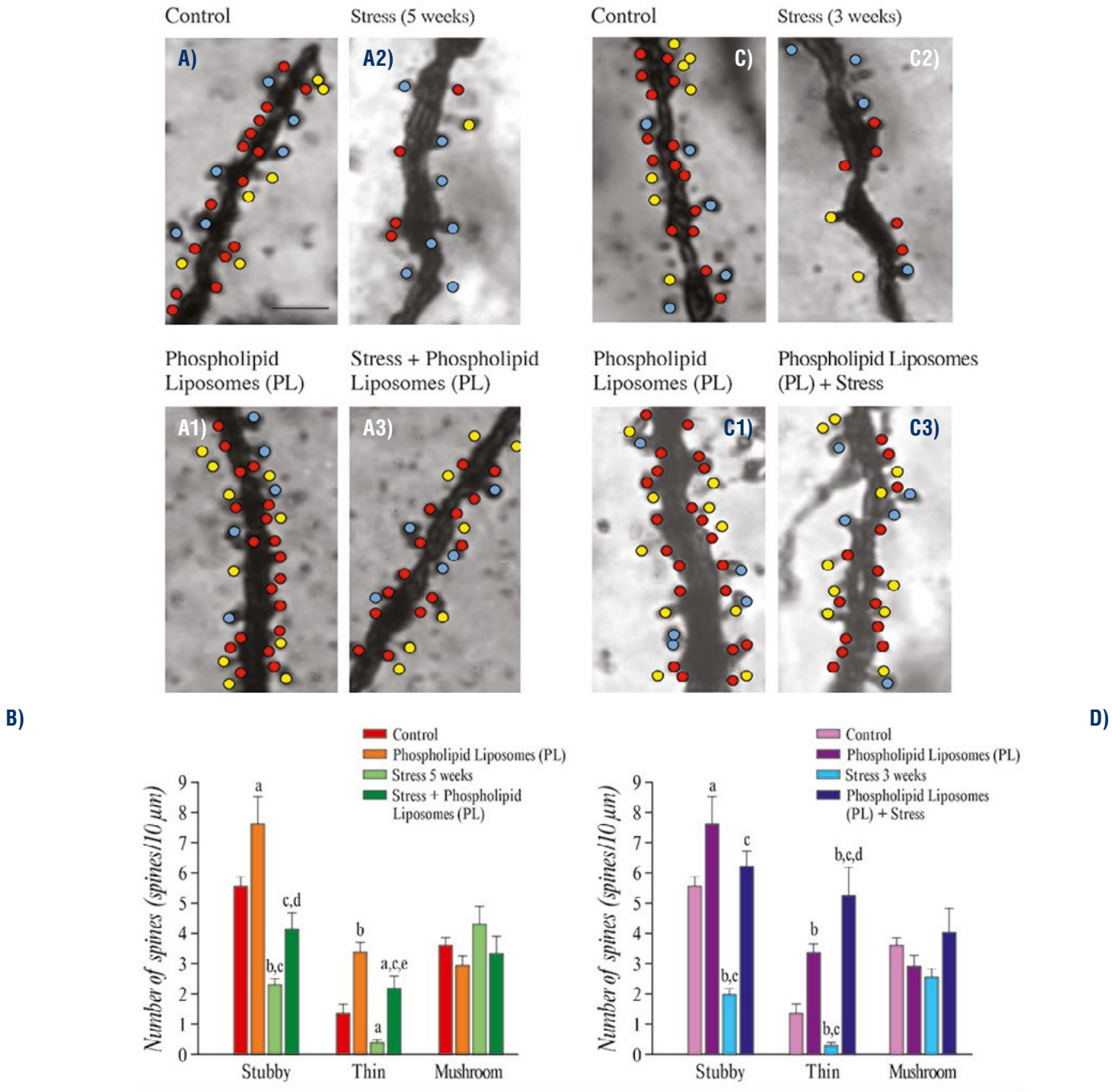


[a] P < 0.001 *vs* control; [b] P < 0.001 *vs* stress 5 weeks; [c] P < 0.001 *vs* stress 3 weeks.

Figure 4.
Chronic treatment with PL reverses **(A, B)** and prevents **(C, D)** the reduction in the number of dendritic spines induced by chronic stress in the hippocampal granule cells of rats. **(A, B)** PL (50 mg/kg for 4 weeks), reverses the effect of stress on dendritic spine density in the hippocampal dentate gyrus. **(C, D)** Pre-treatment (4 weeks) with PL prevents the reduction in dendritic spine density caused by chronic stress (3 weeks). All the data obtained were compared with the group not exposed to chronic stress and treated with a solvent (control). **(A, C)** Images representing the dendritic branches of Golgi-impregnated granule cells of the hippocampal dentate gyrus in which the dendritic spines are evident (scale bar: 5 µm), magnification 100X. **(B, D)** Bar graph summarizing the relative density of dendritic spines measured in the terminal dendrites (3-4 degree) of granule cells. The data are shown as the number of spines calculated in 10 µm of dendrite and represent the mean ± SEM of 5 rats per group (approximately 100 dendritic branches were analysed) analysed using the two-way ANOVA test followed by the Newman-Keuls post-hoc test.

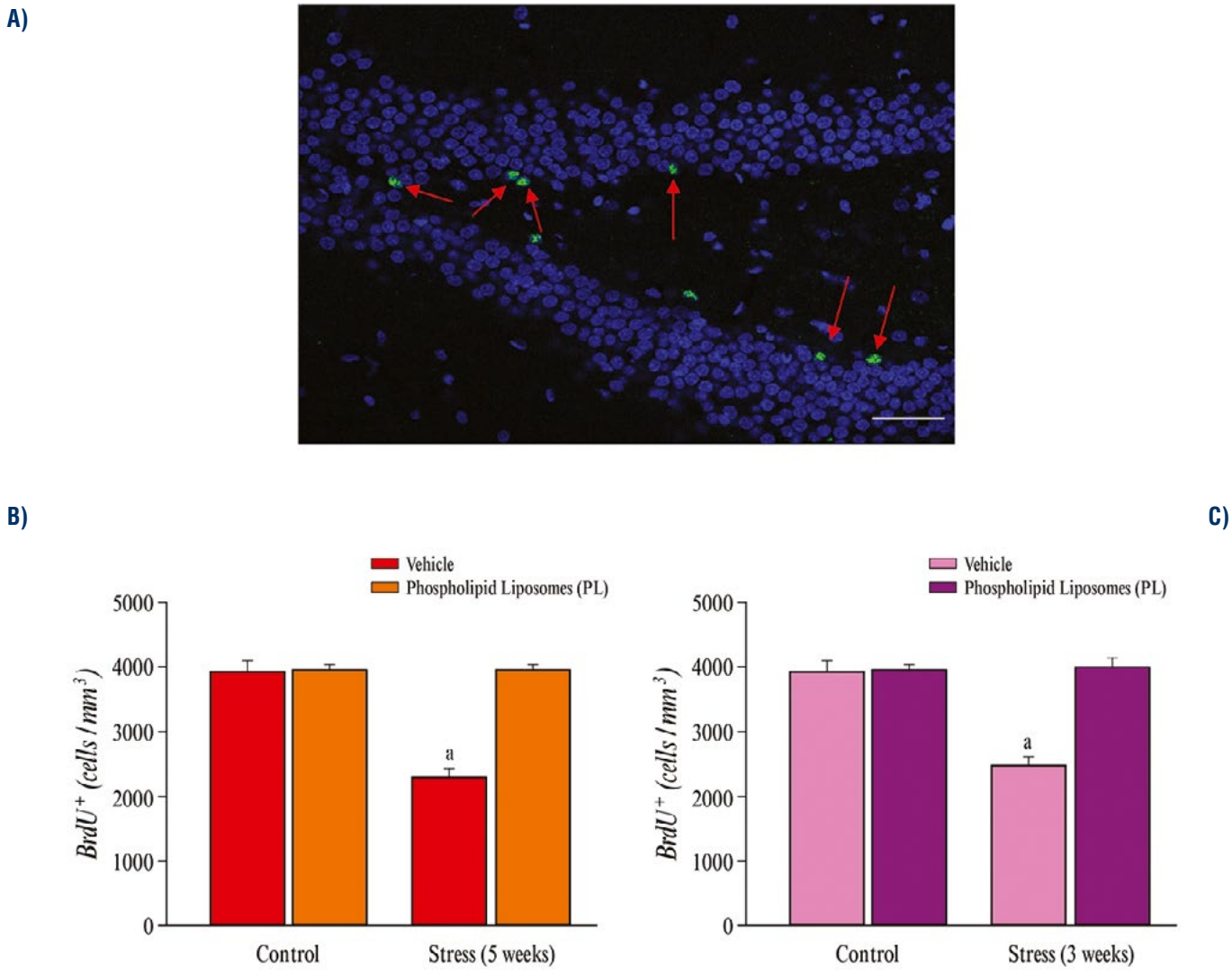
cal specialists, on account of their relative tolerability and ease-of-use in terms of dose and side effects. However, elderly patients are often reluctant to accept pharmacological therapy [67] and may be more vulnerable to the side effects of these drugs (including organ-specific side effects) and drug-drug interactions. Therefore, in order to improve treatment efficacy and tolerability, there is increasing interest in drugs that are chemically different from "classic antidepressants" and can either be used in monotherapy or as an add-on to antidepressant therapy to reduce the latency period and the side effects associated with this kind of treatment [68-72].

LF is indicated as an adjuvant in therapy for altered brain metabolism resulting from neuroendocrine disorders. In this context it can play a primary role since, as stated earlier, phospholipids are involved in various biological func-



[a] P < 0.05 *vs* control; [b] P < 0.01 *vs* control; [c] P < 0.001 *vs* PL; [d] P < 0.05 *vs* stress; [e] P < 0.05 *vs* stress.

Figure 5.
Treatment with PL increases the density of thin and stubby spines and antagonises and prevents the reduction in the density of the same spines **(A-D)** caused by chronic stress. PL (50 mg/kg for 4 weeks) increases the density of thin and stubby spines and reverses **(A, B)** the effect of stress on the morphology of dendritic spines in the hippocampal dentate gyrus. **(C, D)** Treatment (4 weeks) with PL prevents the reduction in stubby and thin spines caused by chronic stress (3 weeks). All the data obtained were compared with the group not exposed to chronic stress and treated with a solvent (control). **(A, C)** Images representing the dendritic branches of granule cells of the hippocampal dentate gyrus labelled using the Golgi silver staining method, in which the dendritic spines (scale bar: 5 µm) are divided according to their morphology into stubby (red), thin (yellow) and mushroom (pale blue) groups using Neuron Studio software, magnification 100X + 10X optical zoom. **(B, D)** The graph represents the density of the dendritic spines labelled using the Golgi silver staining method, measured in the terminal dendrites (3-4 degree) of granule cells. Bar graph summarizing the relative density of spines with different morphology as calculated in a 10µm dendritic section of the different experimental groups. Data are reported as means ± SEM of values from 5 rats/group analysed with one-way ANOVA followed by Newman-Keuls post-hoc test.

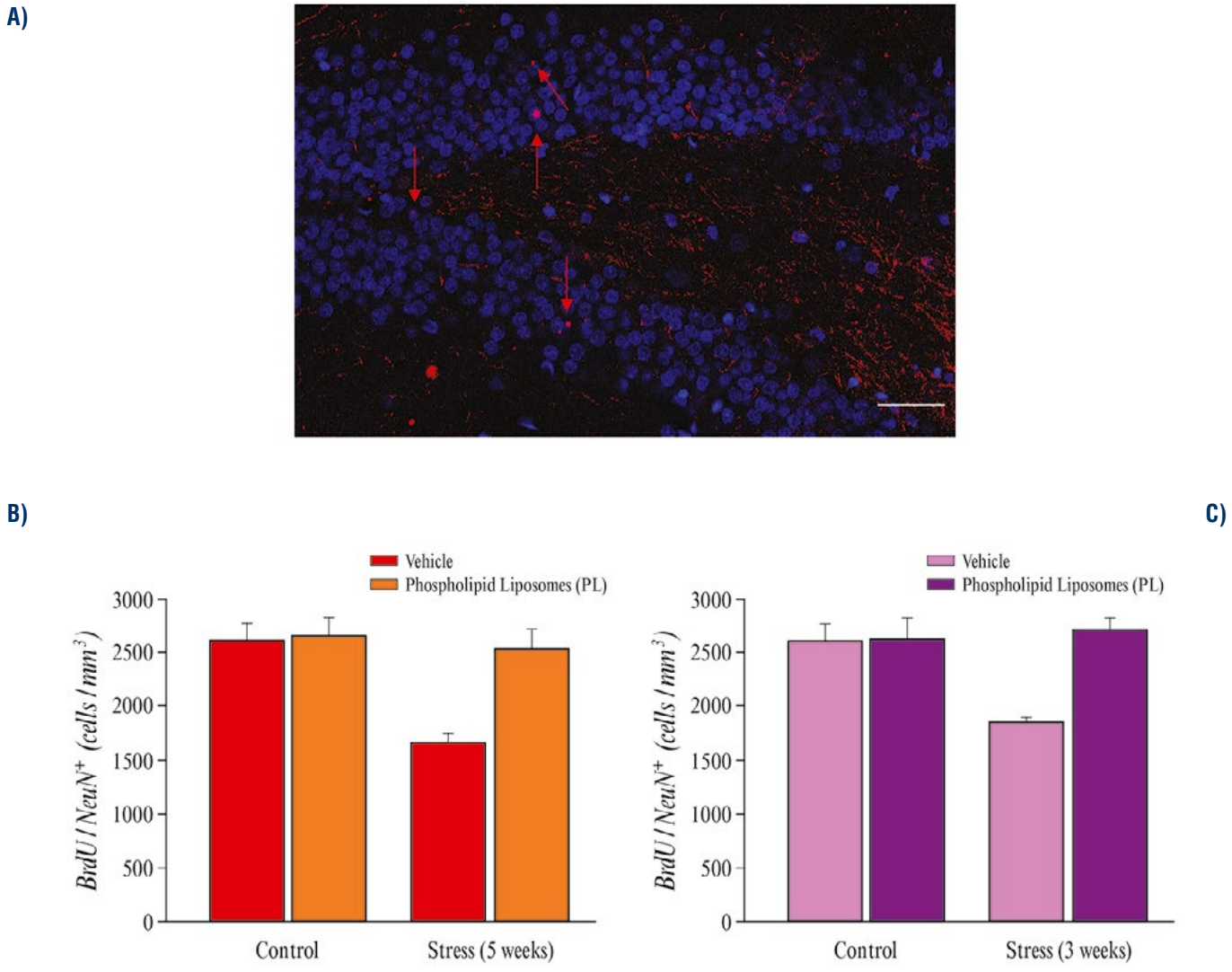


[a]: P < 0.001 *vs* control.

Figure 6.
Chronic treatment with PL reverses and prevents the reduction in the cell proliferation caused by chronic stress in the hippocampal granule cells of rats. Cell proliferation was determined 24 hours after administration of BrdU. All the data obtained were compared with the group not exposed to chronic stress and treated with a solvent (control). **(A)** Confocal representative image of cell proliferation in the subgranular zone of the hippocampal dentate gyrus. Cell proliferation was measured by counting the BrdU-positive cells (green) overlaid with DAPI (dark blue). Arrows indicate positive cells; scale bar: 100 um, magnification 100X. The graphs represent **(B)** the effect of PL in reversing the effect of chronic stress; **(C)** the protective effect of pre-treatment with PL on chronic stress (3 weeks) and show the number of proliferating cells per mm^3 in the subgranular zone of the hippocampal dentate gyrus. The data are shown as the mean ± SEM of positive cells per mm^3 of 5 rats per group analysed using the two-way ANOVA test followed by the Newman-Keuls post-hoc test.

tions [73] and because some areas of the brain in patients with anxiety-depressive symptoms are deficient in phospholipids, which leads to a reduction in cell activity [74].
Numerous clinical studies have been conducted with LF, in order to confirm the efficacy and safety observed in animal models. The main clinical results can be summarised as follows:

- *efficacy in monotherapy*. A double-blind, randomised, placebo-controlled clinical study conducted in 64 menopausal women evaluated the efficacy and safety of LF for the treatment of anxiety and depression. This specific target group was chosen as a possible ideal model for investigating the efficacy and safety of LF in contrasting the neuroendocrine and



[a]: P < 0.001 *vs* control.

Figure 7.
Chronic treatment with PL reverses and prevents the reduction in the neurogenesis caused by chronic stress in the hippocampal granule cells of rats. Cell proliferation was determined 21 days after administration of BrdU. All the data obtained were compared with the group not exposed to chronic stress and treated with a solvent (Control). **(A)** Confocal representative image of neurogenesis in the dentate gyrus. Neurogenesis was determined by counting the BrdU-positive cells (red) overlaid (purple) with the NeuN (dark blue). Arrows indicate positive neurons; scale bar: 100 µm), magnification 100X. Bar graphs represent **(B)** the effect of PL in reversing the effect of chronic stress; **(C)** the protective effect of pre-treatment with PL on chronic stress (3 weeks) and show the number of cells in neurogenesis per mm^3 in the dentate gyrus of the hippocampus. The data are shown as the mean ± SEM of neurons per mm^3 of 5 rats per group analysed using the two-way ANOVA test followed by the Newman-Keuls post-hoc test.

metabolic imbalance that affects mood and behaviour with consequent symptoms of anxiety and depression. The study lasted 60 days with the following dosage: parenteral administration of 2 ml of active drug or placebo on alternate days. Efficacy was assessed using the *Hamilton Anxiety Scale* (HAM-A). At the end of the study there was a significant reduction ($p < 0.001$) in the total HAM-A score in both groups. However, the reduction in HAM-A score was statistically significant in patients treated with LF *vs* placebo at 40 days ($p = 0.006$), 60 days ($p < 0.001$) and the last follow-up visit ($p < 0.001$). These results demonstrate the statistically significant efficacy of LF in monotherapy in reducing mild-to-moderate symptoms of anxiety and depression, as in the case of patients with menopausal syndrome [62,75];

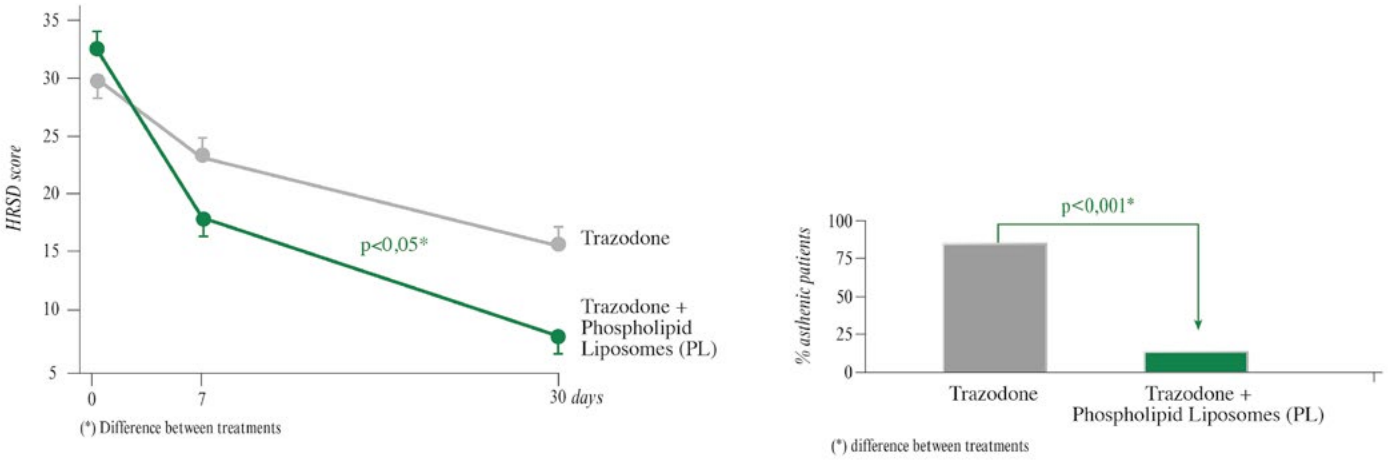


Figure 8.
As an add-on to antidepressant therapy, PLs have been shown to significantly reduce the latency period of the antidepressant ($p < 0.05$) and side effects of antidepressant therapy such as asthenia ($p < 0.001$).

- *efficacy as an add-on to antidepressant therapy*. Patients administered LF parenterally as an add-on to antidepressant therapy, such as sulpiride [62,76], trazodone [62,77] and clomipramine [62,75,76], showed a significant improvement in the symptoms of depression compared to monotherapy with psychotropic drugs, demonstrating that PL potentiate the efficacy of antidepressants; furthermore, LF has been shown to reduce significantly the latency period of antidepressant action and significantly reduce the incidence of side effects such as asthenia from the administration of antidepressants (Figs. 8A, B). These clinical data show a further advantage for clinical practice: the subjective therapeutic benefit experienced by patients at the first sign of improvement in their symptoms is linked to better treatment adherence and compliance [63,80,81]. Lastly, when LF is given as an add-on in therapy with antidepressants such as amitriptyline [80] or clomipramine [63,80,82], it has been shown to have a synergistic effect; patients treated with LF and half doses of antidepressants have obtained similar therapeutic results to those achieved in patients treated with full doses of antidepressants alone. These results are also clinically significant, since a reduction in the dosage of antidepressants is associated with a lower risk of adverse events [63,83].

The results of the clinical studies confirm LF as a clinically valid therapy for managing depressive disorders, both as a monotherapy (mild to moderate) and as an add-on to antidepressant therapy. With its ability to boost the effectiveness of antidepressant therapy, reduce the latency period and decrease the rate of adverse events, LF may be of particular clinical importance in elderly patients, since it can enable the use of lower dosages of antidepressants and reduce the rate of adverse events, which are important factors in these patients.

Conclusions

Brain aging, which begins at varying ages of onset, is characterised by a progressive involution of neurons, both morphologically and functionally, with associated evident changes to the cognitive, emotional and affective spheres, and in physiological sleep patterns.

The build-up of toxic molecules and oxidative stress processes in the brains of elderly individuals often translate as a reduction in neuronal adaptation to negative environmental stimuli, making these subjects fragile in their control of their cognitive and emotional processes. In the last twenty years, super-resolution imaging and molecular technologies have revealed the existence of neuronal atrophy and a reduction in synaptic (dendritic spines) density, along with chemical and physical changes to the membrane, particularly to the phospholipid component [84].

The above data suggest that, in addition to appropriate lifestyle and the absence of chronic stress, age-related brain deterioration may be effectively slowed down by treatments that improve the chemical and physical condition of the neuronal membrane and, consequently, synaptic plasticity. In order to maintain sufficient brain function in later life, neuronal performance must be such that it ensures optimal membrane and synaptic function. One useful method for achieving this may be administration of PL that can reconstitute the efficacy and function of the membrane and therefore promote the neuronal connectivity that have been weakened by ageing [84].

Depressive disorder in elderly patients is a particularly important and complex clinical condition, which clinicians need to address in order to improve diagnostic and therapeutic approaches. After the age of 65, many people are likely to experience the symptoms of a depressive disorder. This probability increases if they have a history of mood disorders, if their health is impaired for other rea-

sons, if they have unfavourable social and environmental circumstances, and, in other words, if they present all the characteristic "fragilities" of the elderly. Mood disorders are not always straightforward to diagnose. This may be because their clinical characteristics are not always evident (masked depression, subthreshold depression), or because there is greater focus on somatic symptoms, or because they are not accurately distinguished from other forms of impairment that related to brain ageing. Neuroscience has improved knowledge of the brain's ageing processes and of the impact of chronic stress on the mechanisms involved in neurogenesis, brain homeostasis, the efficacy of neurotransmission systems and brain plasticity. Also, experimental research models have highlighted the important role played by phospholipids at neuronal level and that low levels of them can impair many brain functions; but also that these can be reactivated by administering a drug made up of neuro-homologous PL. The clinical correlate of this understanding is the role these changes play in the onset and maintenance of depression, mood and anxiety. Failure to identify depression in elderly patients and, consequently, failure to treat it leads to the endurance of a major impairment to health, worsens the prognosis of other disorders, markedly increases the risk of suicide, and reduces life expectancy. The therapeutic approach for elderly patients for whom a depressive disorder has been identified and diagnosed places the spotlight on the issue of the treatment of depression in general. In addition to and alongside psychotherapy, the role of antidepressants such as SSRIs, SNRIs and NaSSAs remains key as first-choice half-dose therapy, with all due consideration for the issues posed for this group by interactions with other drugs, their greater susceptibility to side effects and their intensity, and the duration of the latency period, which is more or less twice that seen in adult patients. This is why, on the basis of the data emerging from experimental models and clinical research on the role of phospholipid, it would appear clinically useful to include PLs in the treatment plans [85] for depression in elderly patients. Treatment with PL in monotherapy (1 ampoule intramuscularly or intravenously, as prescribed) in light-to-moderate depressive disorders with or without anxiety provides the benefit of significantly reducing the symptoms of depression and anxiety, alongside good tolerability and an absence of interaction with other drugs. In more severe depressive disorders, PL can be prescribed as an add-on to major antidepressant therapy with the benefit of reducing the dose of the latter, as per good clinical practice in elderly patients, obtaining a synergistic antidepressant action, with a reduction in the latency period, and increased safety with fewer side effects. The reduction in side effects such as asthenia occurs not only as a result of lower dosages of the major antidepressant, but is also due to the specific action of PL. All these benefits can have a positive impact on treatment adherence and effectiveness, in addition to the advantage of neurotrophic activity and reactivation of neuroplasticity [63].

References

1. Montgomery SA, Beekman ATF, Sadavoy J, et al. Consensus statement on depression in the elderly. J Clin Psychiatry 2000;2:46-52.
2. Altamura AC, Cattaneo E, Pozzoli S, et al. Assessment and pharmacological mamagement of elderly depression. Gior Ital Psicpatol 2006;12:85-92.
3. Copeland JR, Beekman AT, Braam AW, et al. Depression among older people in Europe: the EURODEP studies. World Psychiatry 2004;3:45-9.
4. Istat in cifre - 2015.
5. Baldwin R. Depression in later life. New York: Oxford University Press 2010.
6. Bruce ML, McAvay GJ, Raue PJ, et al. Major depression in elderly home health care patients. Am J Psychiatry 2002;159:1367-74. https://doi.org/10.1176/appi.ajp.159.8.1367
7. Blazer DG. Depression in late life: review and commentary. J Gerontol A Biol Sci Med Sci 2003;58:249-65. https://doi.org/10.1093/gerona/58.3.m249
8. Andreescu C, Reynolds CF 3rd. Late-life depression: evidence-based treatment and promising new directions for research and clinical practice. Psychiatr Clin North Am 2011;34:335-55. https://doi.org/10.1016/j.psc.2011.02.005
9. Giordano A, Rozzini R, Trabucchi M. Frailty in elderly: a clinical view. Giornale di Gerontologia 2007;55:2-6.
10. Volkert J, Schulz H, Härter M, et al. The prevalence of mental disorders in older people in Western countries - a meta-analysis. Ageing Res Rev 2013;12:339-53. https://doi.org/10.1016/j.arr.2012.09.004
11. Biggio G, Brignoli O, Bruni AC. Depressione dell'anziano nell'ambulatorio del medico di medicina generale. Rivista SIMG 2017;(1):1-19.
12. Baldwin R. Depression in later life. New York: Oxford University Press 2010.
13. Pitsillou E, Bresnehan SM, Kagarakis EA, et al. The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. Mol Biol Rep 2020;47:753-70. https://doi.org/10.1007/s11033-019-05129-3
14. Ding Y, Dai J. Advance in stress for depressive disorder. Adv Exp Med Biol 2019;1180:147-78. https://doi.org/10.1007/978-981-32-9271-0_8
15. Keller J, Gomez R, Williams G, et al. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. Mol Psychiatry 2017;22:527-36. https://doi.org/10.1038/mp.2016.120
16. Belanoff JK, Kalehzan M, Sund B, et al. Cortisol activity and cognitive changes in psychotic major depression. Am J Psychiatry 2001;158:1612-6. https://doi.org/10.1176/appi.ajp.158.10.1612
17. Keller J, Flores B, Gomez RG, et al. Cortisol circadian rhythm alterations in psychotic major depression. Biol Psychiatry 2006;60:275-81. https://doi.org/10.1016/j.biopsych.2005.10.014
18. Lembke A, Gomez R, Tenakoon L, et al. The mineralocorticoid receptor agonist, fludrocortisone, differentially inhibits pituitary-adrenal activity in humans with psychotic major depression. Psychoneuroendocrinology 2013;38:115-21. https://doi.org/10.1016/j.psyneuen.2012.05.006
19. Nelson JC, Davis JM. DST studies in psychotic depression: a meta-analysis. Am J Psychiatry 1997;154:1497-503. https://doi.org/10.1176/ajp.154.11.1497

[20] Rock PL, Roiser JP, Riedel WJ, et al. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med 2014;44:2029-40. https://doi.org/10.1017/S0033291713002535

[21] Xu L, Mao R. Neurophysiologic advance in depressive disorder. Adv Exp Med Biol 2019;1180:99-116. https://doi.org/10.1007/978-981-32-9271-0_5

[22] Peng D, Yao Z. Neuroimaging advance in depressive disorder. Adv Exp Med Biol 2019;1180:59-83. https://doi.org/10.1007/978-981-32-9271-0_3

[23] Fang Y. Depressive disorders: mechanisms, measurement and menagement. Adv Exp Med Biol 2019;1180:179-91.

[24] Duman RS, Newton SS. Epigenetic marking and neuronal plasticity. Biol Psychiatry 2007;62:1-3. https://doi.org/10.1016/j.biopsych.2007.04.037

[25] Tylee A, Gastpar M, Lèpine JP, et al. Identification of depressed patient types in the community and their treatment needs: findings from the DEPRES II (Depression Research in European Society II) survey. DEPRES SteeringCommittee. Int Clin Psychopharmacol 1999;14:153-65.

[26] Istituto Superiore Sanità. 2014. www.epicentro.iss.it/temi/mentale/SuicidiItalia2014.asp

[27] Altamura AC. Anxious-depressive syndromes in the elderly. Assessment, clinical course and treatment. In: Racagni G, meraldi E (editors). Anxious depression: assessment and treatment. New York: Raven Press 1987, pp. 209-16.

[28] Naismith SL, Norrie LM, Mowszowski L, et al. The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. Prog Neurobiol 2012;98:99-143. https://doi.org/10.1016/j.pneurobio.2012.05.009

[29] Weisenbach SL, Kumar A. Current understanding of the neurobiology and longitudinal course of geriatric depression. Curr Psychiatry Rep 2014;16:463. https://doi.org/10.1007/s11920-014-0463-y

[30] Sachdev PS, Mohan A, Taylor L, et al. DSM-5 and Mental Disorders in older individuals: an overview. Harv Rev Psychiatry 2015;23:320-8. https://doi.org/10.1097/HRP.0000000000000090

[31] Hegeman JM, Kok RM, van der Mast RC, et al. Phenomenology of depression in older compared with younger adults: meta-analysis. Br J Psychiatry 2012;200:275-81. Interview: reliability and validity according to the CIDI. European Psychiatry 1997;12:224-31. https://doi.org/10.1192/bjp.bp.111.095950

[32] Onder G, Landi F, Gambassi G, et al. Association between pain and depression among older adults in Europe: results from the Aged in Home Care (AdHOC) project: a cross-sectional study. J Clin Psychiatry 2005;66:982-8. https://doi.org/10.4088/jcp.v66n0804

[33] Gallo J, Rabins P, Anthony J, Sadness in older persons:13 years follow-up of a community sample in Baltimore, Maryland. Psychol Med 1999;29:341-50. https://doi.org/10.1017/s0033291798008083

[34] Amore M. Partial androgen deficiency and neuropsychiatric symptoms in aging men. J Endocrinol Invest 2005;28(11 suppl proceedings):49-54.

[35] The North American Menopause Society. Depression, Mood Swings, Anxiety. https://www.menopause.org/for-women/sexual-health-menopause-online/causes-of-sexual-problems/depression-mood-swings-anxiety

[36] Genazzani AR, Monteleone P, Gambacciani M. Hormonal influence on the central nervous system. Maturitas 2002;43(Suppl):11-7. https://doi.org/10.1016/s0378-5122(02)00144-5

[37] Judd LL, Akiskal HS. The clinical and public health relevance of current research on subthreshold depressive symptoms to elderly patients. Am J Geriatr Psychiatry 2002;10:233-8. https://doi.org/https://doi.org/10.1097/00019442-200205000-00002

[38] Petrini M. The rights of the frail elderly: an ethical perspective G. Gerontol 2007;55:15-29.

[39] Forsman AK, Schierenbeck I, Wahlbeck K. Psycho-social interventions for the prevention of depression in older adults: systematic review and meta-analysis. J Aging Health 2011;23:387-416. https://doi.org/10.1177/0898264310378041

[40] Hornsten C, Lövheim H, Gustafson Y. The association between stroke, depression, and 5-year mortality among very old people. Stroke 2013;44:2587-9. https://doi.org/10.1161/STROKEAHA.113.002202

[41] Unutzer J, Patrick DL, Marmon T, et al. Depressive symptoms and mortality in a prospective study of 2,558 older adults. Am j Geriatr Psychiatry 2002;10:521-30. https://doi.org/10.1097/00019442-200209000-00005

[42] Steffens Dc, Levy RM. Sociodemographic and clinical predictors of mortality in geriatric depression. Am J Geriatr Psychiatry 2002;10:531-40. https://doi.org/10.1097/00019442-200209000-00006

[43] Biondi M, Tarsitani L. Stress e spettro dell'umore. In: Cassano GB, Tundo A. Lo spettro dell'umore. Milano: Elsevier Masson 2008.

[44] Minervino A. Introduzione a Medico, paziente e malattia. Giovanni Fioriti Editore 2016.

[45] Brown HA, Murphy RC. Working towards an exegesis for lipids in biology. Nat Chem Biol 2009;5:602-6. https://doi.org/10.1038/nchembio0909-602

[46] Van Meer G, Voelker DR, Feigenson GW. Membrane lipids: where they are and how they behave. Nat Rev Mol Cell Biol 2008;9:112-24. https://doi.org/10.1038/nrm2330

[47] Gallala HD, Breiden B, Sandhoff K. Regulation of the NPC2 protein-mediated cholesterol trafficking by membrane lipids. J Neurochem 2011;116:702-7. https://doi.org/10.1111/j.1471-4159.2010. 07014.x

[48] Buchenauer T, Behrendt P, Bode FJ, et al. Diet-induced obesity alters behavior as well as serum levels of corticosterone in F344 rats. Physiol Behav 2009;98:563-9. https://doi.org/10.1016/j.physbeh.2009.09.003

[49] Lalanza JF, Caimari A, del Bas JM, et al. Effects of a post-weaning cafeteria diet in young rats: metabolic syndrome, reduced activity and low anxiety-like behaviour. PLoS One 2014;9:e85049. https://doi.org/10.1371/journal.pone.0085049

[50] Ortolani D, Oyama LM, Ferrari EM, et al. Effects of comfort food on food intake, anxiety-like behavior and the stress response in rats. Physiol Behav 2011;103:487-92. https://doi.org/10.1016/j.physbeh.2011.03.028

[51] Prasad A, Prasad C. Short-term consumption of a diet rich in fat decreases anxiety response in adult male rats. Physiol Behav 1996;60:1039-42. https://doi.org/10.1016/0031-9384(96)00135-7

[52] Warneke W, Klaus S, Fink H, et al. The impact of cafeteria diet feeding on physiology and anxiety-related behaviour in male and female Sprague-Dawley rats of different ages. Pharmacol Biochem Behav 2014;116:45-54. https://doi.org/10.1016/j.pbb.2013.11.016

[53] LeDoux JE. Emotion: clues from the brain. Annu Rev

Psychol 1995;46:209-35. https://doi.org/10.1146/annurev.ps.46.020195.001233
54 Seligman MEP. Learned helplessness. Annu Rev Med 1972;23:407-12. https://doi.org/10.1146/annurev.me.23.020172.002203
55 Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry 1997;54:597-606. https://doi.org/10.1001/archpsyc.1997.01830190015002
56 Müller CP, Reichel M, Mühle C, et al. Brain membrane lipids in major depression and anxiety disorders. Biochim Biophys Acta 2015;1851:1052-65. https://doi.org/10.1016/j.bbalip.2014.12.014
57 Bruni A, Toffano G, Leon A, et al. Pharmacological effects of phosphatidylserine liposomes. Nature 1976;260:331-3. https://doi.org/10.1038/260331a0
58 Riassunto caratteristiche del prodotto Liposom Forte.
59 Toffano G, Bruni A. Pharmacological properties of phospholipid liposomes. Pharmacol Res Commun 1980;12:829-45. https://doi.org/10.1016/s0031-6989(80)80046-4
60 Horrobin DF, Bennett CN. Depression and bipolar disorder: relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities,cancer, ageing and osteoporosis. Possible candidate genes. Prostaglandins. Leukot Essent Fatty Acids 1999;60:217-34. https://doi.org/10.1054/plef.1999.0037
61 Koprdova R, Bögi E, Belovičová K, et al. Chronic unpredictable mild stress paradigm in male Wistar rats: effect on anxiety- and depressive-like behavior. Neuro Endocrinol Lett 2016;37(Suppl 1):103-10.
62 Biggio G, Mostallino MC, Giusti P, et al. Overview of the pharmacological properties and therapeutic efficacy of phospholipid liposomes (Liposom Forte) in patients with depressive disorders. Minerva Psichiatrica 2018;59:45-53. https://doi.org/10.23736/S0391-1772.17.01955-0
63 Sackeim HA, Roose SP, Burt T. Optimal length of antidepressant trial in later-life depression. Journal of Clinical Psychopharmacology 2005;25:34-7. https://doi.org/10.1097/01.jcp.0000170683.25802.12
64 Reynolds CF 3rd, Frank E, Perel JM, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA 1999;281:39-45. https://doi.org/10.1001/jama.281.1.39
65 Bressi C, Sarotti E, Manoussakis C, et al. Depression in the elderly: risk factors, comorbidity, treatment and prognosis Rivista di Psichiatria 2008;43:1-13.
66 Gareri P, Falconi U, De Fazio P, et al. Conventional and new antidepressant drugs in the elderly. Prog Neurobiol 2000;61:353-96. https://doi.org/10.1016/s0301-0082(99)00050-7
67 Rokke PD, Scogin F. Depression treatment preferences in younger and older adults. J Clin Geropsychol 1995;1:243-58. https://doi.org/10.1097/JGP.0b013e3181cc0350
68 Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. Nature Rev Neurosci 2006;7:137-51. https://doi.org/10.1038/nrn1846
69 Möller HJ, Bitter I, Bobes J. Position statement of the European Psychiatric Association (EPA) on the value of antidepressants in the treatment of unipolar depression. Eur Psychiatry 2012;27:114-28. https://doi.org/10.1016/j.eurpsy.2011.08.002
70 Papakostas GI. Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorders. J Clin Psychiatry 2009;70:18-22. https://doi.org/10.4088/JCP.8157su1c.04
71 Alpert JE, Papakostas G, Mischoulon D, et al. S-adenosyl-L-methionine (SAMe) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. J Clin Psychopharmacol 2004;24:661-4. https://doi.org/10.1097/01.jcp.0000145339.45794.cd
72 Pancheri P, Scapicchio P, Chiaie RD. A double-blind, randomized parallel-group, efficacy and safety study of intramuscular S-adenosyl-L-methionine1,4-butanedisulphonate (SAMe) versus imipramine in patients with major depressive disorder. Int J Neuropsychopharmacol 2002;5:287-94. https://doi.org/10.1017/S1461145702003085
73 Tillman TS, Cascio M. Effects of membrane lipids on ions channel structure and function. Cell Biochem Biophys 2003;38:161-90. https://doi.org/10.1385/CBB:38:2:161
74 Robertson J, Alotaibi HA. Phospholipids, Choline,Serine and Inositol: effects on major depressive disorders. Integrated Healthcare Practitioners 2011;64-7.
75 Rachev E. Efficacy and safety of phospholipid liposomes in the treatment of neuropsychological disorders associated with the menopause: a double-blind, rando mized, Placebo controlled study. Curr Med Res Opin 2001;2:1-6.
76 Aguglia E, Calandra C, Rapisarda V. The effect of hypothalamic phospholipids liposomes in patients treated with sulpiride or haloperidol. Acta Ther 1984;10:133-44.
77 Giannelli A, Rabboni M, Zarattini F, et al. A combination of hypothalamic phospholipid liposomes with trazodone for treatment of depression. An open controlled study. Acta Psychiatr Scand 1989;79:52-8. https://doi.org/10.1111/j.1600-0447.1989.tb09234.x
78 Roncari G, Bilone F, Formigoni B. Combined treatment of clomipramine and hypothalamic phospholipid liposomes in the therapy of affective disorders. Fidia Report 1988.
79 Antignani P, Marchesi GF, Rapisarda V, et al. Studio multicentrico con liposomi di fosfolipidi ipotalamici in associazione ad amitriptilina in pazienti affetti da depressione monopolare 1990 [Internet]. Disponibile alla pagina: www.slideshare. net/MerqurioEditore_redazione/studio-multicentricocon-liposom-forte-in-associazione-con-amitriptilina in pazienti-affetti-da-depressione-monopolare [citato il 21 nov 2017].
80 Casacchia M, Meco G, Pirro R, et al. Phospholipid liposomes in depression: a double-blind study versus placebo. Int Pharmacopsychiatry 1982;17:274-9. https://doi.org/10.1159/000468583
81 Racagni G, Popoli M. Cellular and molecular mechanisms in the long-term action of antidepressants. Dialogues Clin Neurosci 2008;10:385-400.
82 Moreno-Fernandez RD, Tabbai S, Castilla-Ortega E, et al. Stress, depression, resilience and ageing: a role for the LPA-LPA1 pathway. Curr Neuropharmacol 2018;16:271-83. https://doi.org/10.2174/1570159X15666170710200352
83 Gertsik L, Poland RE, Bresee C, et al. Rapaport, Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. Clin Psychopharmacol 2012;32:61.4. https://doi.org/10.1097/JCP.0b013e31823f3b5f