

Review

## Unipolar late-onset depression: A comprehensive review

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### Abstract

**Background:** The older population increases all over the world and so also does the number of older psychiatric patients, which manifest certain specific and unique characteristics. The aim of this article is to provide a comprehensive review of the international literature on unipolar depression with onset at old age.

**Methods:** The authors reviewed several pages and books relevant to the subject but did not search the entire literature because of its overwhelming size. They chose to review those considered most significant.

**Results:** The prevalence of major depression is estimated to be 2% in the general population over 65 years of age. The clinical picture of geriatric depression differs in many aspects from depression in younger patients. It is not yet clear whether it also varies across cultures and different socio-economic backgrounds. Biological data suggest that it is associated with an increased severity of subcortical vascular disease and greater impairment of cognitive performance. Many authors consider the existence of a somatic disorder to be related to the presence of depression in late life, even constituting a negative prognostic factor for the outcome of depression. Most studies support the opinion that geriatric depression carries a poorer prognosis than depression in younger patients. The therapeutic intervention includes pharmacotherapy, mainly with antidepressants, which is of established value and psychotherapy which is not equally validated.

**Conclusion:** A significant number of questions regarding the assessment and treatment of geriatric depression remain unanswered, empirical data are limited, and further research is necessary.

### Introduction

As the older population increases so also does the number of older psychiatric patients. Elderly psychiatric patients

manifest certain specific and unique characteristics. Yet most psychiatrists are trained to diagnose and treat young patients with 'functional' disorders. Thus, they may find it

difficult to evaluate a typical elderly patient whose clinical picture is not exactly in accord with the modern classification systems DSM-IV and ICD-10. The problem of poor recognition of geriatric depression by physicians and nursing staff is well described, and it is suggested that less than half of hospitalised patients with depression in general medical practice are referred to a psychiatrist, and less than one fifth are prescribed antidepressant medication [1]. Yet this illness can have significant consequences. Those who manifest depression have up to 1.5–3 times higher morbidity [2], the lifetime risk of suicide in patients with Major Depression is reported to be 15%, and 10% of them die annually [3]. Patients with Major Depression with psychotic features seem to be at an even higher risk for negative outcomes.

The aim of this article is to provide a comprehensive review of the international literature on unipolar depression with onset in old age. The focus is on depression when manifested as a separate condition (primary) and not within the framework of a broader disorder, like vascular or degenerative diseases.

The text is divided into Epidemiology, Clinical symptomatology, Biological models, Relation with organic mental disorders, Relation with somatic disorders, Prognosis, Therapy and Conclusive remarks.

## Methods

The authors reviewed several pages and books relevant to the subject but did not search the entire literature because of its overwhelming size. They chose to review those considered most significant.

## Epidemiology of Geriatric Depression

The prevalence of major depression is estimated to be 2% in the general population over 65 years of age [4–6]. Eight to fifteen percent of the population over 65 years of age have depressive symptomatology severe enough to meet diagnostic criteria for a depressive psychiatric disorder [7]. However, 25–40% of patients in the general hospital setting have either sub-threshold Major Depressive Disorder (MDD), or meet the criteria for MDD [8], (minor depression included). In residential homes, the accepted value for patients with MDD is approximately 12%, with an additional 30% manifesting a milder form of depressive-like symptomatology [9–14].

The precise estimation of the proportion of elderly individuals suffering from depression is problematic due to methodological issues. Problems include the variability of the clinical picture, and variability in the training and experience of the clinician making the diagnosis and the diagnostic criteria used.

## Clinical Symptomatology

Generally, geriatric depression is considered to be a separate clinical entity. However, systematic research provides little or no evidence supporting this view [15]. It has been reported that patients who manifest depression for the first time in late life, are less likely to have a positive family history for affective disorders compared to younger patients with depression [16,17] and are more likely to manifest structural changes of the CNS [18–20]. Various studies of MDD in elderly adults, reported that mood is more often irritable than depressive [21]. Elderly patients with MDD appear to exhibit certain symptoms more than younger MDD patients. These symptoms include loss of weight, feelings of guilt, suicidal ideation, melancholic type MDD, hypochondriasis as well as a higher frequency of associated symptoms of psychosis [22–26]. However, these findings vary across studies. The ratio of males to females with MDD remains stable across the age spectrum in various studies of depression [19].

Many times, depression has an insidious course and neither the patient nor his/her relatives or therapists can recognise it easily. This is especially true in cases where other serious somatic problems are present [27]. Clinicians should obtain a history from as many reliable sources as possible and critically evaluate this information while considering the entire clinical picture [28]. Somatic symptoms are difficult to assess and, as a general rule, physicians should avoid assigning this symptomatology to an underlying mental disorder. It is highly likely the patient indeed suffers from a true 'somatic' disorder even in cases the physician is unable to diagnose it [29]. On the other hand, it is clear that elderly depressives manifest more somatoform symptomatology, in comparison to younger depressives.

While, depression is common in older patients it still often goes unrecognised. A study of 141 family physicians and general internists found that two thirds of the physicians used no standard test to screen for depression. The two most common laboratory tests ordered were thyroid studies (41.1%) and chemistry panels (37.6%). Selective serotonin reuptake inhibitors were most commonly prescribed for depression (53.2%). It is important to note that 29% reported that they were frustrated when dealing with depressed elderly patients [30].

-The concept of Masked Depression [31] used to be popular in the past, but today it is not accepted by either DSM-IV or ICD-10. However, DSM-IV accepts that the onset of health concerns in old age is more likely to be either realistic or to reflect a mood disorder [29], and thus indirectly leaves space for the concept of masked depression.

**-Depressed Mood** is one of the 'core' symptoms of depression at any age. However, this symptom may be absent in many elderly depressives. Additionally, the presence of a personality disorder may confuse the clinical picture. Usually, elderly depressed patients maintain their ability for emotional responses to positive external events and their mood fluctuates widely and more frequently than is the case in younger patients [32]. In any case, the best way to clarify these issues is personal history, often from an informant.

**-Anhedonia:** Elderly depressives retain an emotional responsiveness to external positive events and profound anhedonia is rare.

**-Psychomotor retardation** is not usually present, and generally is linked with melancholic features or 'vascular' depression.

**-Anxiety:** Anxiety symptomatology in the frame of geriatric depression is not well studied. Usually, definitions and criteria base upon the study of young patients are also applied to the elderly. This approach may not be appropriate. Anxiety in the elderly is rarely present alone and almost never fulfils criteria for a solitary anxiety disorder [33,34]. A careful interview may reveal a pervasive tendency to manifestations of anxiety since early adulthood and many times a diagnosis of a personality disorder is given [22]. Fear of death was considered to be a late-life characteristic, however empirical studies showed that it is most prominent during midlife, in contrast to Erikson's theories [35]. In elderly patients, anxiety is often clinically present as tension, unrest, feelings of insecurity or fear, irritability and intense worry rather than as autonomic symptoms. The definitions and symptomatology of anxiety and depression largely overlap each other. About 38–58% [36] of the elderly suffering from major depression also fulfil DSM criteria for an anxiety disorder. Many authors have suggested that the presence of anxiety in the elderly should be considered as a sign of depression, even in cases, which lack true depressive symptomatology [37].

**-Insomnia:** In the elderly, sleep duration is often shorter and sleep is more fragmented, and this may mislead the physician to overlook this symptom.

**-Loss of appetite:** This symptom is also difficult to assess, especially in individuals living in circumstances whereby the quality of food may be low. On the other hand, true loss of appetite may mistakenly be attributed to low quality of food.

**-Fatigue:** This symptom is usually present, however it may be blamed on old age, and treated with vitamins and other 'antifatigue' drugs. The image of a health insurance

booklet filled with this kind of prescription is extremely common worldwide. A recent study on suicide victims who had asked for professional help concerning their mental health problem before committing suicide, found that the vast majority of GPs who had examined these patients a few months prior to their completed suicide, had prescribed this type of medication for their treatment [38].

**-Thought content:** Feelings of guilt and self-reproach are relatively rare and screening for these feelings may invoke hostility from the patient. Complaints concerning the level of care and the behaviour of staff and relatives are prominent. Feelings of helplessness and hopelessness are common.

**-Suicidal Ideation** Elderly depressed patients may have thoughts of dying including suicidal ideation. Many times this reveals itself indirectly, and therefore is not always easily recognizable. Generally, about 83–87% of elderly suiciders suffer from a mood disorder, with major depression accounting for 65% of cases [39].

Suicide increases with increased age, and this constitutes an important health problem for the elderly. Elderly men are at a higher risk for completing suicide than elderly women. The co-existence of a serious somatic disease, like renal failure or cancer, represents a major risk factor for a well-planned suicide attempt [40]. Other risk factors include loneliness and social isolation, usually as a consequence of bereavement. Some authors suggest that the failure to follow medical advice in serious general medical conditions should be considered a form of 'passive suicide'. 'Rational' suicide plans are not common even in severely ill patients. There is a possibility of acute-onset suicidal plans (after an acute incidence concerning general health e.g. stroke or heart attack) [32].

**-Somatic complaints** and hypochondriacal symptomatology are more frequent in late-life depressives than in younger patients. As mentioned above, the assessment of this kind of symptomatology is extremely difficult, since many times such complaints are the result of actual health problems. Somatic and hypochondriacal complaints with onset in old age may be indicative of an underlying depression [41].

- The existence of **psychotic symptomatology** during a depressive episode is considered to be a sign of poor prognosis and may respond better to electroconvulsive therapy [3]. The usual content of delusions is depressive-aggressive (nihilistic, somatic, of poverty). Auditory hallucinations are less common. The presence of psychotic symptoms may be a prognostic sign of more frequent recurrences [42] (only 10% of patients are symptom-free

after one year) and of a need for repeated hospitalisations [43] (about 2.5 times higher risk for readmission).

**-Neurocognitive disorders** are reported in the international literature to be a usual finding in depressed patients. In elderly individuals there is an increased possibility of the co-existence of depression and dementia, or some other type of 'organic' decline of cognitive disorder. The syndrome of 'pseudodementia' has also been described [44]. This term refers to the manifestation of dementia symptomatology, which in fact is due to depression and disappears after antidepressant therapy. A common finding of everyday clinical practice is the discrepancy between the cognitive complaints of the patient and their neuropsychological evaluation, which may indicate that there is no apparent cognitive disorder [45,46]. The careful assessment of cognitive function may well lead to correct diagnosis and differentiation between dementia and depression. Thus the term 'pseudodementia' may be misleading [47-49]. Indeed, the evidence increasingly suggests that cognitive deficits are a noted concomitant of late-life depression. Of the patients suffering from late life depression, 20% to 50% are estimated to have cognitive impairment greater than that observed in age and education-matched controls [50-52]. The cognitive domains implicated in late life depression include executive function, psychomotor speed, attention and inhibition, working and verbal memory, and visuospatial ability [53-55]. In particular, observed deficits in attention and response inhibition and executive function in this population has led investigators to propose the "executive dysfunction" hypothesis of depression, whereby deficits in this cognitive domain is strongly associated with late-life depression and vegetative symptoms [55]. These deficits are proposed to be subserved by deficits in frontal lobe function. Several investigators have suggested that the cognitive deficits in depressed older adults are of clinical significance given that such deficits have been associated with increased rates of relapse, disability and poorer antidepressant response [56-58].

Hierarchically, dementia should be ruled out before making a diagnosis of depression. Recent reports consider 'pseudodementia' the result of the interaction of depression with other biochemical disturbances of the brain and point to the possibility that the patient may develop dementia in the future [59].

**-Aggressive-agitated behavior** (agitation) is defined as verbally aggressive, physically aggressive or physically non-aggressive behavior that is socially unacceptable, according to the definition proposed by Cohen-Mansfield and Billig [60,61]. Of these three aspects of agitated behavior, verbal aggressiveness is considered to relate to depressed affect in non-demented individuals, or in indi-

viduals suffering from a mild form of dementia [62]. Verbally aggressive behavior includes continuous complaining, the demand for the attention of relatives and the staff, negativistic behavior, continuous asking and shouting. It is possible that the patient may have objective reasons that make him/her manifest agitation. Patients who confound physicians and nursing staff, both diagnostically and therapeutically, may respond well to antidepressant medication [63].

Many of these patients manifest a type of behavior that can be characterized as 'passive-aggressive' or 'self-aggressive'. They refuse to get up from bed, eat, wash themselves, or talk. Also, they often hide important information concerning severe somatic disease and in this way they let it go untreated.

**-Insight** may vary and may be totally absent in cases of agitated or regressed behavior.

It is not yet clear whether the clinical manifestations of depression vary across cultures and different socio-economic backgrounds. Two opposing theories have been proposed. The first suggests that there is a transculturally stable core of symptomatology [64], while on the contrary, the second argues that depression may manifest itself in a different way in patients who do not share a common cultural environment [65]. Many authors believe that there is an increased prevalence of depressive symptomatology (not necessarily clinical depression) in black Americans compared to whites, because socio-economic factors are not usually taken into account [66].

Studies from Japan and Taiwan [67,68] report lower frequency of depressive symptomatology in the elderly population compared with studies from Western Europe and the US. The authors attributed these discrepancies to differences in the structure of the family (larger families with stronger bonds in Japan) and to the increased activity of the Japanese elderly.

As far as the quality of symptomatology and the relative frequency of appearance of individual symptoms in young patients are concerned, studies suggest that Caucasians manifest more affective symptoms (depressed affect), patients from China manifest more somatic complaints (e.g. sleep disorder) and that the Japanese manifest more interpersonal functioning problems (e.g. feelings of rejection by others) [68-71]. However, a particularly well designed study of Krause and Liang [72] suggested that the above conclusions are not valid for elderly patients.

Recent studies suggest that ethnicity may impact the prevalence of suicide. African-Americans manifest the peak of

suicide in the age of 25–29 years, and this peak seems to relate to stressful life events. The same is true for Indian-Americans and Alaskan natives. White males appear to manifest two separate peaks in the histogram of suicide, one during mid-life (mid-life crisis) and one after the age of 80 [73]. In addition to ethnicity, social environment may also impact the prevalence of suicide.

It is highly possible that the marked differences in mental health between ethnic groups reported by some authors might reflect socio-economic and health differentials acting concomitantly and adversely. Inequalities in housing, social support, income and physical health status may account for variation in mood observed between immigrants and locals, and may partly explain differences in life satisfaction. Better social support and housing among 'minority ethnic' elders who live alone might be expected to alleviate social stress and improve mental health and psychological well-being [74].

Although not well studied, religion is another factor that may be associated with depression. A study from the US reported that almost 25% of patients use religion to cope with depression [75], and also religious patients had more stable, supportive and higher social environment and higher intellectual functioning [76].

### Biological models of late-life depression

Neuroimaging studies using Computerized Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Emission Tomography (SPECT) and Positron Emission Tomography (PET) have reported a variety of morphological disturbances, which clearly differentiate late-life depression from depression of younger ages [20,77-82]. The co-localization of atrophies and ischaemic lesions, the fact that they both relate to advanced age and to factors predisposing to vascular disease, and the similarity of the localization of lesions in post-stroke depression has led to the hypothesis that late-life depressives constitute a distinct group of depressed patients, suffering from a mood disorder secondary to ischaemic disease of the neuronal circuits that are involved in the generation and regulation of mood [83].

These findings suggest that late-life-onset depression may be associated with an increased severity of subcortical vascular disease and greater impairment of cognitive performance [84]. More, major depression is more common and more severe in patients with vascular dementia[85].

Neuroendocrinological studies of elderly depressives (Dexamethasone Suppression Test, Platelet Imipramine binding sites, Fenfluramine challenge test, chronobiological studies, sleep etc.) reported results similar to those of younger depressives [86-92]. There may be an association

between vascular lesions detected by the T2 sequence of MRI and reduced number of Platelet Imipramine binding sites in the periphery [93]. Many times results are conflicting, there is a large overlap between patients and controls and in any case these methods are unable to guide clinical practice.

Also interesting, although preliminary, is the report that carriers of the ApoE  $\epsilon$ 2 allele are offered some protection from late onset depression. It is also reported that ApoE  $\epsilon$ 2 delays and ApoE  $\epsilon$ 4 hastens the age of onset of geriatric depression [94]. However, other studies did not observe an association between level of depression and presence of the ApoE  $\epsilon$ 4 allele in older adults [95].

### Relationship of Late-life Depression with Organic Mental Disorders

About 10% of AD patients manifest depressive symptomatology [96]. However, studies report different percentages, ranging between 0% and 87% [97]. It seems that patients suffering from milder forms of dementia verbalize their depression more frequently than patients with more severe dementia. As dementia worsens, depression often remits, possibly because there is a central cholinergic system deterioration underlying dementia, which constitutes the core biochemical feature of AD [98]. Generally it is believed that the coexistence of depression does not affect the course of dementia, and therefore cannot serve as a prognostic sign [99]. A further complication factor is the suggested relationship between geriatric depression and ApoE alleles (mentioned in the previous section), which are also related to AD.

In cases of subcortical dementia, the psychomotor retardation observed may lead to the misdiagnosis of depression. However, in advanced stages of dementia, subcortical cases manifest depression more often than cortical cases (although pure cases are rare). This may be partly due to the increased insight subcortical patients have in comparison to AD patients[100]. In early stages there is no difference in depressive symptomatology between cortical and subcortical dementias.

There are several potentially lethal diseases that may have depressive or depressive-like symptomatology as their only early manifestations. In most cases it is not true depression but instead there is a feeling of indifference, apathy or fatigue. Depressed affect is usually absent. Such diseases include neoplasms, vitamin deficiencies, endocrine disorders, toxic and infectious encephalopathies, and metabolic disorders [101].

### **Relationship of Late life Depression with Somatic Diseases and their Treatment**

Many authors consider the existence of a somatic disorder to be related to the presence of depression in late life, even constituting a negative prognostic factor for the outcome of depression [102]. As mentioned, the existence of a severe somatic disease is also considered a risk factor for suicide. These observations may lead to the conclusion that there is a cause-effect relationship between somatic disease and depression in late life, or vice-versa. Disability, particularly physical handicap, may be a prime cause of depression onset in late-life, with genetic predisposition, early adversity and serious life events compounding the relationship. Effective prevention of late-life depression requires attention to maintaining the community infrastructure and support[103].

Percentages of comorbidity between depression and physical illness vary from 6% to 45% [104,105]. The large discrepancy reflects the difficulty in the application of operationalized criteria for the diagnosis of depression in patients with general health problems.

Greater overall severity of medical illness, cognitive impairment, physical disability and symptoms of pain or other somatic complaints seem to be a more important predictor of Major Depression than specific medical diagnoses [106]. Compared with patients without depression, those with minor depression are more likely to report non-health-related stressors during the year before hospital admission. It is generally believed that during hospital admission, certain psychosocial, psychiatric, and physical health characteristics of older medical patients place them at high risk for different levels of depression. Patients with major and minor depression resemble each other more than they do patients without depression[107].

The patient who suffers from a severe somatic disease may not be treated early or sufficiently because of his/her family environment and also because therapists often consider depressive symptomatology to be a 'natural' reaction to the general medical condition. Even when acknowledging the presence of depression, therapists may be pessimistic regarding the outcome of antidepressant medication treatment in geriatric populations. However, antidepressant medication has fair effectiveness in these patients and is effective even in post-stroke depression [108].

On the other hand, depression and disability tend to track together, and most changes occur within the first 6 months after discharge. Patients with a history of depression were less likely to experience improvement in depression unless disability improved [109]. Yet opinions differ concerning the effect of disability on different factors,

such as mild neurocognitive disorders [110]. On the other hand, the fact that many therapeutic agents of various somatic disorders may trigger or exacerbate depression, or even transform it to a refractory form, is well recognized. Examples of these agents are amantadine, antipsychotics, atropine, benzodiazepines, cimetidine, clonidine, cytotoxic agents, digitalis, guanethidine, immunosuppressive agents, insulin, levo and methyl-dopa, nifedipine, propranolol, steroids, stimulants and reserpine [111]. Additionally, patients often use alcohol and other substances of abuse to self medicate their depressive symptoms; this may trigger or exacerbate depression and possibly transform it to a refractory form of depression.

### **Prognosis for late-life depression**

The appearance of depressive symptomatology in advanced age is often accompanied by lack of family history of affective disorder, presence of cognitive deficits, brain atrophy, white matter lesions and increased mortality [112,113]. Similar to depression in younger individuals, late-life depression is characterized by exacerbations and remissions. Millard proposed the 'rule of thirds' concerning the prognosis of geriatric depression [114]. That is, regardless of the therapeutic intervention employed, approximately one-third of patients will manifest remission, another third will remain symptomatic in the same condition and the rest will worsen. The research that followed revealed that almost 60% of elderly depressives would manifest at least one recurrence in the future. Chronic or continuously recurrent depression affects almost 40% geriatric depressive patients [115].

Most studies support the opinion that geriatric depression carries a poorer prognosis than depression in younger patients [116]. However many authors attribute this, to factors like failure to make an early diagnosis and improper or insufficient treatment [117,118]. Poor prognostic factors for depression in younger patients include female gender, premorbid personality and family history of affective disorder [119]. For patients with geriatric depression, the prognosis is more dependent on physical handicap or illness and lack of social support, however further research on this issue is needed [120].

The final piece of the puzzle concerns reports suggesting that the psychological trauma, which develops upon the experience of an early parental loss contributes to the development of depression even in old age. The loss of mother for men and father for women early in life is a predictor of late-life depression. The most probable explanation is that these early losses make individuals vulnerable to stressful events, and as they age they become increasingly vulnerable to late life losses and stressors[120-122]. The role of stressors in life as independent predictors of depression in old age needs further investigation [123].

Overall, it appears that almost 25% of elderly subjects suffering from depression will eventually manifest full remission of symptomatology, either spontaneous or after some kind of treatment, and will maintain this ideal condition for a long period of time. Another 25% will not respond to any kind of intervention and will continue to manifest severe depressive symptomatology. The other 50% will manifest either partial remission, or experience periods of time free of symptomatology, interspersed with frequent exacerbations of depression [124].

### **Therapeutic intervention**

The review of studies concerning the clinical manifestations of late-life depression reveals difficulties in the assessment of the efficacy of therapeutic methods that are available. The complexity of the clinical picture makes the selection of 'pure' patients very difficult. Thus, there are only a few studies available for the therapist to rely on, in order to design therapeutic intervention in a valid and reliable way. However, such 'pure' patients are usually not found in everyday clinical practise. That is, the literature points out the efficacy of therapeutic methods, giving less weight to their effectiveness, which is what matters in clinical practise.

### **Pharmacotherapy**

Several important questions exist considering pharmacotherapy for late-life depression.

#### **- Does it make a difference?**

In their review of the literature, Gershon et al., identified only 25 placebo-controlled studies concerning antidepressant medication in elderly individuals, published between years 1964 and 1986, despite flexibility of criteria for study inclusion [125]. Efficacy is generally well documented, although careful review indicates that the difference between the active agent and the placebo is small and significant residual symptomatology remains in most patients [126,127]. Stoudemire et al., reported that although 90% of patients recovered from their index episode of depression, relapse rates were approximately 29% [128].

#### **- Which agents are more suitable for use in elderly patients?**

Montgomery et al observed equal efficacy between a serotonin reuptake inhibitor and a norepinephrine one [129]. Also, cases refractory to one class of agents, also proved to be refractory to the other one. Studies reporting superiority of a specific agent over another often are not replicated. The only stable finding is a different side-effect profile between different groups of agents.

#### **- Which dose and for how long should be administered in order to achieve the optimum therapeutic response?**

The aging process changes the absorption rate, the distribution and the metabolism and excretion rate. The most important changes concern liver and kidney function. Although the variability across subjects is large [130,131], the changes generally result in an increase in the serum levels of the substance [132] and a larger half-life. Additionally, as age increases, the ratio of fat to muscle also increases [133] and this results in an increase in the volume of distribution of most psychotherapeutic agents. So, there is a variety of changes of the pharmacodynamics in the elderly, and these changes may push towards opposite directions. Thus, the end result is not always 'a priori' known.

#### **- Is it possible to predict the response or the side effects by using neuroimaging techniques or biological markers?**

It is widely believed that the existence of high signal lesions in brain CT or the T2 sequence of brain MRI, characterize patients at increased risk for development of delirium or cognitive disorders after treatment with tricyclic antidepressants (TCA's) or electroconvulsive therapy (ECT) [83]. However, at this time, accurate predictions using CT or MRI regarding response to somatic therapy or risk for delirium or cognitive disorders are not able to be made.

Continuation therapy seems to demand the same dose of medication that produced improvement, and not a lower one [134]. The application of prophylactic pharmacotherapy seems to reduce the risk for relapse by 2.5 times in comparison to placebo [78], in spite of the fact that almost 30% of patients under prophylactic pharmacotherapy eventually relapsed.

A significant problem with the pharmacological approaches to geriatric depression appears to be the patient's compliance. Approximately 70% of patients receive only half of the recommended dose [135]. Even when they comply, it is not unusual for older depressed patients to forget to take their pills or to change the timetable or even to overmedicate themselves or worse, abuse medication [136]. Also, the rate of dropout is very high and reaches even 50%. Many authors think that the increased prevalence of side effects is responsible for this. It is true, that elderly patients suffer more often from urinary retention, glaucoma and constipation. Coexisting disorders of the barosensors [137] and the blockade of  $\alpha$ 1-adrenergic receptors by antidepressants may cause dizziness, orthostatic hypotension and falls. Sedation due to the antihistaminic action is common. The risk of cardio-

vascular complications is also increased [138], because antidepressants possess quinidine-like properties. Finally, the effect of pharmacotherapy on the quality of life of these patients is not well investigated.

Vision disorders in this population may also play a role, since the patient may not be able to read the instructions or even the labels, and hearing problems may lead to misunderstandings regarding dosage and regimen.

The attitude of the clinician towards the therapeutic intervention and effort is important also. A study that assessed the attitudes of 89 geriatricians and 72 geriatric psychiatrists by searching their prescription habits, reported that geriatricians tended to undermedicate patients and to prescribe medication for smaller durations than needed. The same was true for psychiatrists who felt their training in prescribing medication for the elderly was insufficient [139].

### 1-Tricyclic Antidepressants (TCAs)

Tricyclic Antidepressants (TCA's) [140] are considered to act initially through inhibiting norepinephrine and serotonin and to a lesser degree dopamine reuptake. Their anticholinergic properties may cause cognitive disorders, delirium, constipation, dry mouth, blurred vision and increased intraocular pressure (in cases of pre-existing glaucoma). Anti-alpha1-adrenergic properties are responsible for orthostatic hypotension phenomena that could lead to falls and hip fractures. Antihistamine properties are responsible for sedation. Several reviews reported that TCAs, in spite of their efficacy in the treatment of late-life depression, have so many undesirable effects, that their use in the treatment of elderly patients is limited [1,141,142].

### 2-Selective Serotonin Reuptake Inhibitors (SSRI's)

SSRIs exhibit mild side effects in comparison to TCAs, and patients tolerate them better. It is reported that this leads to adequate dosage prescription and better compliance [143]. The most frequent side effects are sexual dysfunction, gastrointestinal symptoms like nausea, vomiting, diarrhea, insomnia, anxiety and agitation. More recent studies dispute these agents to be as effective as TCAs, especially in more severe cases of depression.

### 3-Other antidepressants

Like Mianserin, Mirtazapine, Moclobemide, Nefazodone, Venlafaxine may also be effective in the treatment of geriatric depression, and all have some limited support from controlled studies.

**4-Combinations of antidepressants:** The use of combinations of antidepressants is a very common everyday clinical practise. Usually the combination of an SSRI and a TCA is used in patients with refractory depression. However, combinations may be dangerous due to toxicity from the higher plasma levels of the TCAs [144], and because of the inhibition of cytochrome P450 induced by the SSRIs [145].

**5-Lithium** is not well studied in geriatric patients. The coadministration of lithium with an SSRI is supposed to be a potentially lethal combination, because it may cause central serotonin syndrome [146], but this is rather rare and careful monitoring of the patient reduces risk. However a specialist is needed and it is not recommended for General Practitioners.

### 6-Other biologic therapies

- **Psychostimulants** [147,148] like methylphenidate [149] and d-amphetamine have been used in inpatients who could not receive proper antidepressant therapy because of their general medical condition, or because an imminent response is absolutely necessary. The international literature is extremely limited concerning this matter and there are no controlled studies. Also, psychostimulants may elicit agitated or psychotic symptomatology, instead of an antidepressant effect.

- **Thyroid hormones** have been used in combination with TCAs [150] and SSRIs [151]. Results are reported to be positive.

- **The increase of bioavailability of antidepressants with the coadministration of lithium** [152] (augmentation) has been attempted, but there are many critics concerning effectiveness and safety.

- **Electroconvulsive therapy (ECT)** [153,154] is recommended for geriatric depression, according to the directives of the American Psychiatric Association. Since there are plenty of therapeutic agents available today, it is not recommended as the first choice. It is generally considered safe and it is preferable to leaving the patient without treatment. The greatest risk is for patients with a stroke, and is not recommended for them until they are six months post-stroke. The coexistence of an 'organic' brain disorder might lead to the development of delirium after ECT application which may last for several weeks. Many authors consider ECT to be the sole true therapy for delusional late-life depression.

### Psychotherapy

Pessimism still dominates the mind of psychotherapists who follow the classical Freudian psychoanalytical the-



ory, which considers elderly patients to be refractory to psychotherapy because of the accumulation of life events. Today this cannot be easily accepted. However, it is not only psychotherapists who consider elderly patients unsuitable for psychotherapy [155]. The patients themselves may conceive this kind of therapy as a sign of weakness, because they find it necessary to drop life-long defences in front of a therapist who is usually younger.

It has been suggested that psychotherapy aimed at depressive ideation and rehabilitation efforts focused on instrumental activities of daily living might improve the outcome of geriatric depression [156]. Impairment in instrumental activities of daily living was significantly associated with advanced age, severity of depression, and medical burden. The relationship of depressive symptoms to impairment in instrumental activities of daily living is not influenced by age or medical burden. Anxiety and depressive ideation as well as retardation and weight loss are significantly associated with impairment in instrumental activities of daily living. Impairment in instrumental activities of daily living appears to be a relatively independent dimension of health status that is related to depressive symptoms, particularly anxiety and depressive ideation as well as retardation and weight loss. However there are specific points that make the application of these techniques very difficult. Patients with severe neurocognitive disorder, psychomotor retardation or impairment of the sensory organs (making communication difficult) are not suitable to enter demanding psychotherapeutic procedures. Severe symptomatology due to the general medical condition, like physiological instability may also restrict the therapeutic manoeuvres or significantly delay the process. It seems that a dogma could be expressed: almost any patients could accept and benefit from some form of psychotherapeutic intervention, adjusted to his/her specific problems and needs [157]. The most common model of geriatric psychotherapy does not aim to cure, but instead with how to deal and cope with problems.

The negative attitude against psychotherapy among older adults is an important problem. Generally, it is recommended to be one of the first issues to be discussed. The patients' attitude should be registered, problems solved and complaints, claims and desires clarified. The patient should be briefed in a comprehensive way as much as possible, adjusted to his/her cultural and educational background or to his/her peculiarities. Furthermore, the therapist ought to be more energetically involved during the psychotherapy of an elderly patient and potentially guide the patient more than in the case of a younger patient.

Another important point that might become a cause of adverse events is the age of the therapist. Usually he/she is

younger than the patient. This fact could give rise to a specific form of transference and countertransference. The patient may pronounce the therapist 'my child' and in other instances could project a down validating attitude against him/her (e.g. 'you can not understand me, only when you turn my age will you understand' etc). Elderly depressives with narcissistic structure of personality may express a negative attitude against younger therapists motivated by feelings of envy. The therapist himself could feel great anxiety or compassion towards the patient, either because of the patient's general health status or simply because of his/her old age, and subsequently avoid touching important matters that could cause distress to the patient (death, weakness, loneliness etc.). Deeper feelings of guilt in the therapist, which are results of previous conflicts (ambivalence) towards parental figures, could activate an overprotective attitude towards the patient.

### Conclusive remarks

The hierarchical approach to mental disorders, which was especially proposed by Kraepelin is very difficult to apply in psychogeriatric patients who by definition suffer from biological disorders without this being a sufficient condition to exclude the diagnosis of a 'neurotic' disorder (the term 'neurotic' is used here with its traditional meaning). Both classification systems do not preclude the co-existence of two or more mental disorders simultaneously (comorbidity). Also these disorders could well be 'qualitatively' distinct (according to more traditional concepts). The same time, a core feature in these systems' phenomenological approach is a hierarchical approach, which demands a step-by-step recognition and assessment of organic (biological) disorders (especially of the CNS) which should be ruled out as causative factors, before the diagnosis of a 'functional' disorder is made. However, when elderly subjects are assessed, this approach is difficult and therapeutic decision becomes relatively unreliable. Partly, this is the cause of worse prognosis for psychogeriatric patients. In the final analysis, the above simply reflects a deficit in our knowledge.

The results of the Epidemiological Catchment Area Study suggested a lower prevalence of depression in elderly subjects in comparison to younger subjects. However an in-depth study of these results show that it is possible these findings are misleading and that the data and interpretation of the results reflect an artefact product of the inappropriateness of the diagnostic criteria for this population.[158]

It could be suggested that the sole use of a categorical way of diagnosis (yes-no) is not sufficient. An additional approach based on the quantification of the symptomatology in more than one dimension seems to be necessary, particularly in older patients. This double approach could

assist a more precise diagnosis and better therapeutic design. It has been initially proposed by Van Praag [159] and already applied by Kay in his prominent theory on schizophrenia [160].

This double approach does not include any kind of a priori theoretical approach, and does not imply nor preclude the continuum between 'normal' state and mental disorder. Especially in the elderly, where the 'normal' changes of both mental and somatic condition interact with 'pathological' changes, both with similar manifestations, this advanced approach could prove particularly helpful. A polarization between an "organic" mental disorder and a 'functional' mental disorder is usually seen in late life. However, one should have in mind that while in some cases these factors are polarized, in others they may be highly interactive.

The difficulty lies mainly in the initial phase of the evaluation, when the examiner tries to decide whether the subject suffers or not from a mental disorder, and if yes, which disorder. Elderly subjects, deprived from abilities and interests, may experience a variety of adverse feelings, especially under the burden of stressful life events. These feelings of sadness, anger, fear etc. could be considered to be 'normal' both from the patient and his environment. The diagnostic threshold should be low enough, because many authors suggest that when a mental disorder appears in late life it could have milder symptomatology. But special caution should be exercised in order not to diagnostically label problems of everyday living.

From a therapeutic point of view, the available methods are far from satisfactory. Elderly patients have high rates of dropout. Although the rate of adverse effects is higher than that in younger patients, the use of agents with a milder side-effect profile does not seem to improve compliance, it simply changes percentages of drop-out attributed to each cause. This observation ought to attract the attention of the scientific community and become the focus of further study, since it is estimated that almost half of patients for whom a pharmaceutical treatment is recommended, finally do not follow any kind of treatment, and the reasons for this remain elusive. An approach could be to shift the focus of interest from agents with less adverse effects to those that could prove to be more effective. There is evidence that intensive intergrated pharmacotherapy with psychotherapy may be more effective than usual standard treatment [161].

A significant number of questions regarding the assessment and treatment of geriatric depression remain unanswered. Since the biochemical substrate of geriatric depression is suggested to be different from that of depression of younger adults, antidepressants that combine the

favourable side-effect profile with the modification of multiple transmitter systems could prove valuable. However of even higher importance is the development of agents that lack significant drug-to-drug interactions (since most elderly receive a number of agents for the treatment of somatic diseases), have limited adverse effects and are neither sedative nor activating. When psychotropic medications are utilized, it is crucial to choose the agent with a more favourable side effect profile.

Currently, empirical data are limited, and further research is necessary in order to improve our ability to diagnose and treat geriatric depression.

### Conflicts of interest

None declared.

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