Treatment of Depression in Elderly: The Challenge to Success

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Abstract: Depression in the elderly is a major challenge to current Psychiatry and a major mental health problem for several reasons, including its clinical atypicity (hampering a correct diagnosis), its greater severity and risk of suicide. The success of drug treatment will depend on a suitable assessment of the risk-benefit balance. In this review, we will address the antidepressants with a favorable side effect profile, because the elderly have a higher sensitivity to them. Antidepressant treatment in the elderly has a number of peculiarities: it should start with lower doses than those recommended for adults, it is preferable to the use of antidepressants without anticholinergic and sedative effects, to prevent cognitive impairment and risk of cardiotoxicity; it should evaluate possible interactions with other drugs, since the elderly are usually polymedicated patients with different somatic comorbidities; if antidepressant response is obtained, the drug should be kept for long periods, even for lifetime. There is a wide arsenal of antidepressant drugs with mechanisms of action focused on enhancing monoaminergic transmission. An alternative to these classical mechanisms of action is given by agomelatine, a melatoninergic agonist drug. In this paper, we discuss the pharmacodynamic and pharmacokinetic profiles of these agents that may have an influence on the efficacy, tolerability and safety of treatment in the elderly. The use of antidepressants in the elderly should be performed only when necessary, but age should not deprive the patients of medication to improve their health and quality of life.

Keywords: Depression, elderly, treatment, drug therapy.

INTRODUCTION

Depression in the elderly is a major problem of mental health and also the main challenge for psychiatry area. Their atypical clinical profile difficult their correct identification; its greater severity and its high risk of suicide constitute additional prognoses and therapeutic problems. Furthermore, depression in the elderly is accompanied by high costs and difficulties of health care.

According to the World Health Organization (WHO), depression is the most frequent mental disorder among geriatric patients [1]. From the quantitative point of view, it is estimated that 12% of subjects over 65 years old treated ambulatory have one major depressive episode (DSM-IV-R), while 20% show significant depressive symptoms that substantially reduce quality of life [2]. However, the prevalence of depression in this group varies greatly, depending on the social and clinical circumstances in which the elderly are found. Its prevalence ranges from 6% to 18% among geriatric primary care patients, and it is higher on medical inpatient services or in nursing homes [3-7]. Despite the high depression prevalence in elderly, it is estimated that clinically significant depression is often under-recognized, and it goes untreated or not adequately treated in 40–60% of cases [7, 8].

The treatment of depression in elderly people need antidepressant drugs with a more favorable benefits/risk ratio due to its greater sensitivity. The treatment of depression in senile age should take into account the following general recommendations: depressive symptoms should be treated in all cases with an antidepressant agent; in order not to worsen cognitive symptoms, it is preferable to use anti-depressants without anticholinergic/sedative effects; avoiding cardiovascular effects of antidepressants, especially heterocyclic drugs; consider the physical or somatic comorbidity and possible interactions with other prescribed drugs; treatment should start with half dose than in young adults and kept in accordance with the criteria of duration of treatment [2, 9].

PHARMACODYNAMIC ASPECTS IMPLICATED IN EFFICACY AND TOLERABILITY OF ANTI-DEPRESSANT DRUGS

In the last six decades, the monoamine hypothesis has been the pharmacological target for the treatment of depression. At this moment, all antidepressants, including the presynaptic receptor antagonist mirtazapine, continue to use the same mechanism of action as the classic drugs, that is, the modulation of monoaminergic neurotransmission at a synaptic level [10].

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Table 1: Pharmacodynamic Aspects Implicated in Efficacy and Tolerability of Antidepressant Drugs

Pharmacological Effect	Drugs	Therapeutic Effect	Adverse Effects
5-HT uptake inhibition	TCAs SSRIs Venlafaxine Nefazodone	Antidepressant	Nausea, Nervousness, Insomnia, Sexual dysfunction
NA uptake inhibition	TCAs Venlafaxine Reboxetine	Antidepressant	Tachycardia, Hypertension, Tremor, Sexual dysfunction
5-HT receptors agonism			
5-HT_{1A} postsynaptic	TCAs MAOIs SSRIs Mirtazapine Nefazodone	Antidepressant Anxiolytic	
5-HT_{1D}	SSRIs		Headaches, migraines
5-HT_{2}	SSRIs	Antidepressant Antiobsessive Antibulimic	Insomnia, Anxiety, Sexual dysfunction, Agitation, Akathisia
5-HT_{3}	SSRIs		Loss appetite, Increase gastrointestinal motility, Nausea, Diarrheas
Presynaptic 5-HT_{1A} receptors desensibility	TCAs SSRIs Venlafaxine	Antidepressant	
5-HT receptors antagonism			
5-HT_{1D} presynaptic	Pindolol	Antidepressant	
5-HT_{2}	TCAs Mirtazapine Nefazodone Agomelatine	Antidepressant, Improvement sexual function	Hypotension
5-HT_{3}	Mirtazapine	Antiemetic	
Blockade central and peripheral muscarinic cholinergic receptors	TCAs Paroxetine (SSRIs)		Blurred vision, Constipation, Dry mouth, Urinary retention, Tachycardia, Memory disorders
Histaminergic (H_1) receptors antagonism	TCAs Mirtazapine		Sedation, Drowsiness, Dizziness, Weight gain, Hypotension
Adrenergic receptors antagonism			
Central an peripheral α_1 receptors	TCAs		Orthostatic hypotension, Dizziness, Tachycardia, Sedation
α_2-receptors	TCAs	Antidepressant	Priapism
Down-regulation β-adrenergic receptors	TCAs Fluoxetine Fluvoxamine Paroxetine Venlafaxine Nefazodone	Antidepressant	
Monoamine oxidase inhibition	MAOIs	Antidepressant	Hepatotoxicity, Hypertensive crisis, Headaches, Iirritability disorders, Insomnia, Sexual sphere disorders

MAOIs: Monoamine Oxidase Inhibitors; SSRIs: Selective Serotonin Reuptake Inhibitors; TCAs: Tricyclic antidepressants; NA: Noradrenaline.

Currently, there is considerable scientific data, from both animal and human experimentation, supporting the participation of non-monoaminergic mechanisms in the physiopathology of depression. Attempts to find antidepressants that initiate their effects through non-monoaminergic mechanisms are intense but discouraging. However, one of the landmarks in this sense is the advent of agomelatine, an antidepressant with agonistic action on MT_1 and MT_2 melatonin receptors. Furthermore, agomelatine by blocking 5-HT_{2C} receptors increases norepinephrine and dopamine levels in prefrontal cortex. This agent did not block other neurotransmitter receptors [10, 11].

The pharmacodynamic profile of antidepressants, especially its ability to inhibit the reuptake of monoamines and its affinity for different neurotransmitter receptors, determines its efficacy, safety and tolerability profile (Table **1**).

ANTIDEPRESSANT EFFICACY IN LATE-LIFE DEPRESSION

Despite the high depression prevalence in elderly, the number of clinical trials in this population is scarce. However, in the last two decades there is a tendency to increase studies in late-life depression.

Recently, Kok *et al*. [12] carried out a systematic review and meta-analysis of 92 double-blind randomized controlled trials (RCTs) of acute phase treatment of older depressed patients, 51 of which were pooled into one of the meta-analyses. In this meta-analysis, as we can see in previous reviews, all classes of antidepressant (tricyclic antidepressants, TCAs, selective serotonin reuptake inhibitors, SSRIs, and other antidepressants) were individually more effective than placebo in achieving response (48.0% treated with antidepressants *vs.*38.6% in patients using a placebo). However, in achieving remission, only pooling all three classes of antidepressants together (33.7% of patients) showed a statistically significant difference versus placebo (27.2% of patients).

Studies comparing different classes of antidepressants did not indicate differences in achieving response or remission between TCAs and SSRIs or other antidepressants [12, 13]. This was also the case in more severely depressed patients [12], in contrast to other studies that indicate a better efficacy of TCAs among inpatients [14]. In general, late-life depressed patients were found to respond to all classes of antidepressants, but with a small effect [12, 15], especially when they were compared with adult patients with major depressive disorder (MDD) [16]. In conclusion, antidepressant treatment in older depressed patients is efficacious and there are not differences in effectiveness between different classes of antidepressants [12].

On the other hand, a number of socio-demographic and clinical features have been found to moderate antidepressant efficacy in elderly population. Those variables could help clinicians for a more individualized treatment. In male elderly, a worse treatment outcome was found with antidepressants and also in the sub-group treated with SSRIs. This reduced response was also seen in elderly with a longer mean duration of the current episode. On the contrary, a higher response rate was found in patients with a higher baseline severity and in those patients treated at their first episode of illness [7]. This could be possibly due to side effects, especially in old patients who usually have high rates of discontinuation [17]. Moreover, age effects on some neurotransmitter factors, such as serotonergic function, have been hypothesized to modulate antidepressant response [18].

In relation with the maintenance treatment of depression in elderly, there are few controlled studies. The duration of maintenance therapy is variable, and may become undefined. The existing consensus on the duration of the pharmacotherapy of maintenance in the long term after a first episode of depression is limited, and most experts recommend 6-12 months of drug treatment after a first episode of depression in old people [19, 20]. In a follow-up period of depression in the elderly from 2 to 3 years, recurrence rates range between 50% and 90% [21]. Thus the goal of treatment is not only acute recovery, but also the prevention of the recurrence [22].

It has been described that the treatment-resistant depression affects up to one-third of the elderly patients with depression. The current age, the highest levels of acute or chronic stress factors, less social support, earlier age of onset, melancholic-like demonstrations, patients needing use of adjunctive medication in acute treatment, and the highest level of current anxiety were also factors that predicted a worse long-term response [20, 23].

Since the efficacy of all antidepressants versus placebo is demonstrated and the effectiveness of different antidepressants is similar in the elderly, selection is not conditioned by differences in efficiency,

but by other factors as the profile of adverse effects, comorbidities and concomitant use of other drugs that can produce drug interactions.

SELECTION OF THE ANTIDEPRESSANT DRUG ACCORDING TO ITS PHARMACODYNAMIC PROFILE

In general, all antidepressants have a similar efficacy, even in elderly. Thus we must select the right antidepressant according to the profile of adverse effects. This is of great importance to individuals with comorbid somatic pathology. Changes in the function and cerebral structure that are related to aging increase the vulnerability to the undesirable effects of antidepressants. The loss of neurons in cortex, locus coeruleus and hippocampus increases the sedative and psychomotor effects of drugs. The gradual loss of cholinergic neurotransmission in the central nervous system (CNS) increases the sensitivity to the anticholinergic effects of antidepressant. Reduction in the sensitivity of the carotid and hypothalamic centers facilitates the hypotensive effect of antidepressants. Loss of the number of neurons in the nigrostriatal pathway increases the extra pyramidal effects of some drugs [2].

In fact, adverse effects that would be intolerable for a particular patient may be used therapeutically in others. Thus, mirtazapine, an antagonist of presynaptic α_2–adrenergic receptors and a potent antihistaminic, can facilitate sleep and increase appetite and weight. These properties may be of particular interest in elderly patients with insomnia or weight loss [24]. In contrast, bupropion or reboxetine inhibit reuptake of catecholamines and can energize patients showing an excessive lassitude [25].

Also, treatment with trazodone has been usually used, mainly in low doses (e.g. 25-50 mg), for the treatment of insomnia associated with depression. Trazodone can produce sedation and orthostatic hypotension at doses used in young adult [26]. In contrast, bupropion can produce agitation and insomnia, which can be useful in patients with lethargy, fatigue or with excessive sedation during the day [2, 9]. Selective inhibitors of the reuptake of serotonin and norepinephrine (SNRIs), as duloxetine, may be useful in depressed patients with neuropathic pain. Nausea, agitation, insomnia and hypertension appear more often at high doses [2, 13].

Several clinical guidelines and the National Institute for Health and Clinical Excellence [27] recommend that the choice of an antidepressant should be guided by consideration of side effects and the patient's preferences. In general, SSRIs (citalopram, escitalopram, sertraline, fluvoxamine, paroxetine, fluoxetine) constitute the first line treatment for depression in the elderly. Paroxetine and fluoxetine are highly effective, but due to the long half-life of fluoxetine and the potent anticholinergic effect of paroxetine, they would not be the first line treatment of depression in the elderly patient.

TCAs are effective in the elderly patient, but they are not considered first choice, given their adverse effects and cardiotoxicity in case of overdose [28, 29]. This class of antidepressants should only be used in patients with previous good response to treatment with TCAs [9]. The TCAs are contraindicated in patients with a recent history of myocardial infarction, defects of cardiac conduction, glaucoma, orthostatic hypotension, urinary retention, hypertrophy of prostate or cognitive impairment [2, 28, 30].

Monoamine oxidase inhibitors (MAOIs) have a narrow therapeutic margin and require restrictions with several drugs and nutrients that content tyramine. This group of antidepressants is not recommended in the elderly even if it is performed by personnel with experience in this type of antidepressants [2, 31].

THE ROLE OF COMORBIDITY AND ADVERSE EFFECTS IN THE ANTIDEPRESSANT SELECTION IN ELDERLY

The under-representation of elderly people in clinical trials of antidepressants and the fact that most of such trials have short term follow-up periods, make difficult to derive reliable or precise estimates of the adverse events incidence in this group. This problem is further compounded when criteria for trials exclude elderly people with comorbid conditions. Although several observational studies have examined different adverse outcomes associated with use of antidepressants, few have been specific to an older population [32].

To give a proper focus to antidepressant use in elderly, it must be considered its predictable adverse effects to look for therapeutic alternatives. In this sense, the blockade of several neurotransmitters receptors in the CNS by antidepressants produce a series of secondary adverse effects, like excessive sedation, hypotension, cardiotoxicity, proconvulsant and anticholinergic effects [33, 34].

The study of the effect of antidepressants on cognitive function is difficult because cognitive dysfunction is aninherent clinical component in depression. At central level, anticholinergic effect of TCAs is related to loss of cognition, even in elderly without basal cognitive deterioration in form of blockade of the word, confusion, delirium and memory disorders [34, 35]. Furthermore, several studies have shown that TCAs, MAOIs or paroxetine anticholinergic properties may worsen cognitive function. In contrast, other antidepressants have showed its usefulness to treat the cognitive deficits, or that at least do not worsen them, like SSRIs, SNRIs and mirtazapine. In addition, it seems that these improvements depend on whether patients are responders or not to antidepressant treatment [36].

In some countries, it is not easy to investigate the actual conditions of elderly people's sexual life and, therefore, studies on this matter have been relatively insufficient. However, the elderly have their own personal desires and we cannot improve the quality of life of the elderly without considering sex, which is one of the basic instincts of human beings. Sexual dysfunction associated with antidepressant treatment is a serious side effect that may lead to early end of treatment.

Patients treated with SSRIs and the SNRI venlafaxine have significantly highest rates of overall sexual dysfunction, including desire, arousal and orgasm than patients treated with placebo. Data from 63 studies with more than 26,000 patients treated with second generation antidepressants showed a similar risk of sexual dysfunction among included antidepressants. However, bupropion had a statistically significantly lower risk of sexual dysfunction and both escitalopram and paroxetine showed a statistically significantly higher risk of sexual dysfunction than some other antidepressants [37]. On the other hand, agomelatine may be the most beneficial in patients who suffer from sexual dysfunction or elderly populations who are vulnerable to adverse events [38]. Therefore, mirtazapine, bupropion or agomelatine can be recommended as their sexual side effects are minimum, which can be important for some elderly [39-41].

The cardiovascular adverse effects of the antidepressants are probably the best studied, especially with overdoses of TCAs. In fact, different clinical guides do not recommend the use of TCAs in patients with cardiovascular risk, arrhythmias, heart failure or coronary insufficiency. In these cases, the use of SSRIs, bupropion or mirtazapine is recommended as alternative [42]. Peripheral antimuscarinic properties can induce a slight tachycardia, in which they take part in addition to the norepinephrine reuptake inhibition. Its administration can lead to electrocardiographic alterations, like prolongation of spaces PR, QRS and QT that usually are innocuous in the healthy young, but which can cause a bundle branch blockin elderly. TCAs are implicated in these effects and paroxetine has anti-cholinergic properties similar of the imipramine [2, 43].

The cardiovascular risk is lower with SSRIs than with TCAs in patients with myocardial infarction [44]. The better cardiovascular tolerability of SSRIs, especially the lowest risk of relapse of myocardial infarction, could be explained by the depletion and decreased of serotonin stored in platelets, so dimmed its aggregation. This effect is related to the inhibitory potency of reuptake of serotonin, being more patent with fluoxetine, sertraline and paroxetine [45].

Taylor *et al*. [46] recommend that the use of TCAs should be abolished in patients at risk of developing cardiovascular diseases, such as diabetes, smoking, arterial hypertension, overweight. Reboxetine, duloxetine and venlafaxine must be used with caution in patients with hypertension, while the TCAs, trazodone, and venlafaxine should be avoided in patients at risk of arrhythmias.

However, the risk of cerebral infarction associated with SSRIS is known. Indeed, Trifiro *et al*. [47] in a longitudinal study, conducted in almost 1,000 European patients with more than 65 years, showed an increased risk of stroke in patients who received a SSRI in relation to those who did not receive it. Interestingly, this risk was not increased among patients who were treated with ADTs or other antidepressants. Furthermore, increased risk of cerebral infarction occurred in a database of American patients, treated with SSRIs. However, this risk was not due to hemorrhagic accidents [48]. Similarly, in a case-control study involving 916 patients with intracerebral or subarachnoid hemorrhage, SSRIs was not related with this pathology [49]. It is interesting to note that increased risk of stroke by SSRIs is not related to its platelet antiaggregant activity since the risk of hemorrhagic accident was not increased [50].

From the clinical point of view, there is evidence that some pathophysiological elements in depression

and metabolic endocrine syndrome (MS) are common and may often overlap MS is a group of abnormalities (abdominal obesity, dyslipidaemia, dysglycaemia and hypertension) that predispose a person to develop type 2 diabetes mellitus and cardiovascular disease. People with MS are twice as likely to die for this cause, and three times more likely to develop myocardial infarction or stroke compared to people without MS. Studies in patients with depression suggests that the prevalence of MS is higher in these patients than in healthy controls [51-53].

Secondary amines of the TCAs have been associated with an increase in plasma levels of glucose, such as desipramine or nortriptyline, which inhibit the reuptake of norepinephrine. This fact can be dangerous in diabetic subjects [54]. In contrast, SSRIs can lower blood glucose and weight in depressive patients with diabetes [54]. However, an exception is paroxetine that can alter glycemic control [55]. Duloxetine can increase glucose levels in fasting, observed in some patients with diabetic neuropathy [56]. Also, desvenlafaxine and venlafaxine have been associated with an increase in the levels of glucose [57] or with a neutral behavior. Finally, mirtazapine has been associated with an increase in weight and increased levels of glucose [58]. In contrast, bupropion was related to a decrease in blood glucose, to stimulate the secretion of insulin in subjects with elevated blood glucose and show a favorable effect decreasing the weight in obese subjects [59].

The presence of diabetes in patients with depression is so common that some authors have questioned the role of antidepressants in this problem. In fact, some cohort studies show that the use of antidepressants was associated with an increased risk of diabetes. However, this risk was mitigated when the data were adjusted in accordance with risk factors for diabetes, cholesterol, hypertension and body mass index. With these corrections, the use of TCAs increased the risk of diabetes by 26%, while the use of SSRIs increased the risk by 10%, which is considered by the authors as a moderate risk [52, 53].

TCAs have been associated with a higher rate of dyslipidemia and abdominal adiposity and therefore with a more severe symptomatology of the MS [60]. Imipramine has an unfavorable profile since it increases the total cholesterol/HDL-cholesterol ratio [61]. The antidepressants mirtazapine, venlafaxine and desvenlafaxine have been associated with an increase in relation to LDL/HDL-cholesterol [53, 57, 62, 63]. SSRIs show a favorable lipid profile [59] with the exception of paroxetine, since it raises levels of LDL-cholesterol and triglycerides, [64]. In contrast, fluoxetine presents a favorable lipid profile even in non-depressed diabetic patients [53, 59].

The changes of body weight are a hallmark of depression, which can be shared with different somatic diseases and increased by various antidepressants. The TCAs increase the body weight even at low doses. Similarly, there are multiple references and controlled studies in relation to mirtazapine-induced weight gain [25]. Histaminergic blockade, which induces an increase in appetite for hydrocarbon, could explain weight increase, although this is not the only mechanism [65]. Acute administration of SSRIs has a neutral behavior on body weight [59]. However, Sussman *et al.* [66] showed that the administration of fluoxetine, paroxetine or sertraline for more than 16 weeks led to an increase in weight, clinically significant in 13.8% of the patients.

On the other hand, bupropion is related to a decrease in weight, mainly in subjects with a high body mass index (BMI) [67]. Moreover, in randomized clinical trials, a greater weight increase of 7% occurred in 5% of patients treated with agomelatine, in 5.4% of venlafaxine-treated, 8.8% of SSRI-treated, and 5.7% of the patients in the placebo group [68].

The association between the TCA and hypertension has been suggested by some studies [69]. In addition, SNRIs, as venlafaxine or duloxetine [70], induce an increase of blood pressure, as well as a sustained diastolic increase [59, 71]. However, SSRIs are usually considered neutral agents on blood pressure, while taking into account their broad employment [72], cases of hypertension and hypotension have been described [59].

Currently, there are about 15 epidemiological studies that show the existence of a risk of high digestive bleeding with SSRIs. This risk is magnified with the association of non-steroidal anti-inflammatory (NSAIDs) and the use of proton pump inhibitors can be protector [73]. However, a case-control study conducted in Italy confirmed the gastrointestinal bleeding risk with SSRIs and venlafaxine, even in patients not receiving NSAIDs, corticosteroids, anticoagulants or antithrombotics [74]. Furthermore, the clinical relevance of the risk of bleeding with SSRIs was observed in a study conducted in 520 patients of orthopedic surgery [75]. Therefore, it is recommended

precaution in patients treated with SSRIs in individuals with risk of digestive bleeding [27] or co-treated with NSAIDs or other anticoagulants [73].

Some antidepressants, mainly SSRIs, SNRIs and to a lesser extent TCAs, can induce an excessive release of antidiuretic hormone (ADH). The excess of ADH secretion cause a hyponatremia which translates clinically by malaise, nausea, headache, lethargy, muscle pain, confusion, loss of consciousness and seizures, named "syndrome of inappropriate secretion of ADH" (SIADH) [76]. Although it can be considered a rare adverse effect, some studies indicate that in elderly treated with SSRIs analytical hyponatremia is present in 12 to 25% of patients [77], of which 9% have clinical symptomatology [78]. Since the SIADH occurs in the first month of treatment with SSRIs [79], and also with venlafaxine, it is recommended to control the levels of sodium in the elderly, to prevent its evolution towards more serious complications. The mortality rate among elderly patients with hyponatremia may reach 25% [80]. A possible alternative in patients with SIADH is mirtazapine [81].

Some studies have shown that the use of SSRIs was associated with a statistically significant increase in the risk of osteoporotic fractures, compared to controls without antidepressants [82-84]. The risk with SSRIs is higher than with TCAs and other antidepressants. There is a clear association between the degree of inhibition of serotonin reuptake and the risk of osteoporotic fracture. Serotonin transporter has been located in osteoclasts, osteoblasts and osteocytes and its inhibition has been linked to alterations in the architecture, density and bone mass [85].

ANTIDEPRESSANTS DRUGS INTERACTIONS IN ELDERLY

Regarding interactions, it is advisable to consider the epidemiological frequency of the combination, the frequency of interaction when drugs are co-administered, the therapeutic index of interacting substances (ratio between the therapeutic and toxic levels) or the possibility of establishing an individualized posology (Table **2**).

There is a great interest on drug interactions with antidepressants due to the broad therapeutic arsenal and the longer life expectancy of patients. Comorbidities have increased dramatically the number of described cases of drug interactions [50]. For this reason, it is very important to detect the clinically important interactions. So, antidepressants can cause pharmacokinetic and pharmacodynamic interactions with drugs with a low therapeutic range and used frequently in elderly as digoxin, theophylline, NSAIDs, oral antidiabetics, insulin or anticoagulants, alcohol and other psychoactive drugs. A good knowledge of interactions helps not only to stop the prescription, but also to provide alternatives [2, 86].

SAFETY OF ANTIDEPRESSANTS IN OVERDOSE

The risk of antidepressants overdose is increased in the elderly. The high risk of suicides in this population (especially from 75-80 years) and the physical and cognitive limitations increase errors in dosage [9] (Table **3**). The highest risk is related to the cardiotoxicity, being the potentially most dangerous TCAs and SSRIs are the safest. The TCAs toxicity is very fast: in an hour arrhythmias, seizures, hypotension and coma may appear [87]. In the intoxication with SSRIs akathisia, tremor, agitation, hyperreflexia, delirium, fever, diarrhea, convulsions, clonus, hypertonia, tachycardia and mydriasis predominate. The presentation is mixed among the TCAs and SSRIs with dual antidepressants. Venlafaxine produces seizures and QRS prolongation in 13% and 36% of the patients respectively [2, 88].

CONCLUSIONS

In the heterogeneous group of elderly is necessary to perform anadequate therapeutic, to consider the possibility of physiological changes. These changes do not always flow in parallel with the chronology of the age. The somatic comorbidity, very common in this age group, requires to establish compatible treatments. Similarly, in the elderly with an altered response of several organs, the concentrations of drugs in the tissue targets favor the emergence of adverse reactions. It is necessary to know the habits of the patient, use of tobacco, alcohol and caffeine, as well as the administration of other drugs, indicated for other pathologies or self-medicated, since they can modify the kinetic behavior of psychoactive drugs and cause interactions. Elderly should begin treatment with doses lower than usual and increase them slowly up to the therapeutic dose. Simple dosing regimen facilitate adherence. The use of medications in the elderly should be performed only when necessary, but age should not deprive the patient's medication that improves their health and quality of life. However, many

Table 2: Antidepressant Drugs that may be Involved in Drug Interactions in Elderly

	CYP1A2	CYP2C19	CYP2D6	CYP3A4
Substrates	Amitriptyline		Citalopram	
	Clomipramine	Citalopram	Desipramine	Citalopram
	Desipramine	Clomipramine	Duloxetine	Fluoxetine
	Duloxetine	Fluoxetine	Fluoxetine	Fluvoxamine
	Imipramine	Imipramine	Fluvoxamine	Mirtazapine
	Fluvoxamine	Mirtazapine	Nefazodone	Nefazodone
	Mirtazapine		Paroxetine	Sertraline
	Venlafaxine		Trazodone	Trazodone
	Caffeine		Venlafaxine	Venlafaxine
	Clordiazepoxide		Aripiprazole	Alprazolam
	Clozapine		Codeine	Buspirone
	Diazepam		Donepezil	Carbamazepine
	Haloperidol		Galantamine	Clonazepam
	Olanzapine		Haloperidol	Codeine
			Risperidone	Diazepam
				Quetiapine
				Triazolam
				Ziprasidone
Inductors		Carbamazepine		Carbamazepine
	Carbamazepine	Phenobarbital		Corticosteroids
	Phenobarbital	Phenytoin		Phenobarbital
				Phenytoin
	Phenytoin			*Hypericum perforatum*
Inhibitors	Citalopram+	Fluoxetine++	Bupropion++	Duloxetine+
	Escitalopram+	Fluvoxamine+++	Citalopram+	Fluoxetine++
	Fluoxetine+	Nefazodone	Escitalopram+	Fluvoxamine++
	Fluvoxamine+++	Paroxetine+	Desipramine±	Mirtazapine+
	Mirtazapine±	Sertraline+	Duloxetine+	Nefazodone+++
	Paroxetine+	Valproate	Fluoxetine+++	Paroxetine+
	Sertraline+		Fluvoxamine+	Sertraline+
			Mirtazapine±	Erythromycin
			Paroxetine+++	
			Sertraline+	Haloperidol
			Venlafaxine±	Ketoconazole
			Celecoxib	Nifedipine
			Valproate	

The inhibitors of CYP450 isoforms have been classified with different degrees of inhibition and its potential clinical effect in interaction: ± minimum; + low; ++ moderate; +++ high.
Adapted from Rajji *et al*. [4], and Álamo *et al*. [53].

Table 3: Mortality Risk in Overdose by Antidepressant Drugs

Relatively safe (< 10 deaths /10^6 prescriptions)	Lofepramine
	Mianserine
	Fluoxetine Fluvoxamine
Potentially dangerous (> 10 deaths /10^6 prescriptions)	Clomipramine
	Trazodone
Clearly dangerous (> 20 deaths /10^6 prescriptions):	Phenelzine
	Imipramine
Very dangerous (> 30 deaths /10^6 prescriptions):	Maprotiline
Unacceptable risk (> 40 deaths /10^6 prescriptions):	Dothiepin
	Amitriptyline
	Tranylcypromine

Modified from Ellenhorn [89], and Álamo *et al*. [2].

of the data comment in this review originate from randomized trials whose methodological features may not generalize to the real world of clinical practice.

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