SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS IN THE TREATMENT OF DEPRESSION

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Abstract

Depression is a very common pathological mental condition. It can occur at any person and at any age being a disorder in growing frequency. Depression affects about 10-12% of Western population and is currently among the top five diseases in the world.

Serotonin and norepinephrine reuptake inhibitors (SNRI) are second generation antidepressant drugs. Due to their dual mechanism of actions, these compounds may offer improvements in efficacy and fewer side effects.

The study of two classes of antidepressants: serotonin and norepinephrine reuptake inhibitors SNRI (duloxetine, venlafaxine) and selective serotonin reuptake inhibitors SSRI (citalopram, escitalopram) showed that SNRIs are as effective or have a modest efficacy advantage compared to SSRIs and their side effects are slightly less severe. The SNRIs are used as second-step treatment being prescribed by doctors to patients suffering of depression resistant to other drugs or recurrent depressive episodes. The SNRIs are currently among the most widely used antidepressants behind the SSRI escitalopram.

Key words: depressive disorders, dual reuptake inhibitors, duloxetine, venlafaxine, neurotransmitters, synaptic cleft.

INTRODUCTION

Depression is the most common pathological mental condition. It can occur at any person and at any age being a disorder in growing frequency.

Although the causes of depressive disorders have been widely investigated they remained unclear, concluding that depression occurs due to a combination of factors: genetic factors and childhood experiences that most often lead to the onset of depressive disorders in adult life, stress, environmental factors and biochemical factors (Loo H., Loo P., 2003; http:// www.saptamanamedicala; Gelder M. et al., 1994).

Depression affects about 10-12% of Western population (9-12% in Europe, 10% in USA) showing a women-men ratio of 2:1. One in four women and one in ten men can expect to develop depression during their lifetime (http://healthy.kudika.ro; Lemke L.T. et al., 2013; National Institutes of Health, 2000; National Institutes of Health, 2003). According to the World Health Organization (WHO), depressive disorder is currently among the top five diseases, predicting for 2020 to reach the second place after the cardiovascular diseases (Udriştoiu T. et al., 2011).

MATERIAL AND METHOD

Serotonin and norepinephrine reuptake inhibitors (SNRI) are second generation antidepressant drugs exhibiting dual activity on serotonin reuptake transporter SERT and norepinephrine reuptake transporter NET. SERT and NET are membrane proteins that are responsible for the presynaptic reuptake of serotonin and norepinephrine. Blocking these two types of transporters results in increased concentrations of these neurotransmitters into the synaptic cleft and increased neurotransmission which can alleviate the symptoms of depression (Cashman J.R., Ghirmai S., 2009; http://www.mayoclinic.org).

The purpose of this paper was a comparative study between serotonin and norepinephrine reuptake inhibitors SNRI and selective serotonin reuptake inhibitors SSRI. Even if the SSRIs (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) have dominated the anti depressant market since 1980s, the dual-action antidepressants such as nontricyclic SNRIs (e.g. venlafaxine, duloxetine, milnacipran, des venlafaxine, levomilnacipran) possessing more than one functional activity incorporated into the same molecule may offer improvements in efficacy and fewer side effects (Cashman J.R., Ghirmai S., 2009; Spina E. et al., 2008; Gutierrez M.A. et al., 2003). This article has two sections: in the first part we conducted a theoretical study of the two classes of antidepressants based on literature data, followed in the second part by the comparative study of some SNRI and SSRI drugs issued by medical prescriptions in a community pharmacy in Oradea city between 2008 and 2014.

RESULTS AND DISCUSSION

Currently, the SSRIs are considered first-line agents in the treatment of depression. These compounds selectively inhibit the presynaptic reuptake of serotonin by SERT blocking with no action on other neurotransmitters or other receptors (α_1-adrenergic, H_1-histaminergic or cholinergic M). Thus, they do not show adrenergic, H_1-histaminergic and cholinergic-type side effects (Lemke L.T. et al., 2013; Cristea A.N., 2005). There is evidence from animal and human studies suggesting that combining both serotonin and norepinephrine reuptake inhibition may increase the efficacy of SSRIs (Baron B.M. et al., 1988; Nelson J.C. et al., 1991). Newer antidepressants such as SNRIs acting on both serotonergic and adrenergic systems have shown to be effective in depression, highlighting the role of norepinephrine in the depressed mood (Lemke L.T. et al., 2013; Thase M.E., 2008). Moreover, none of the SNRIs showed significant affinity to other receptors (α_1, α_2, β_1, β_2-adrenergic, cholinergic M, H_1-histaminergic, or benzo diazepine binding sites) in preclinical studies offering a side effect profile

more comparable to an SSRI. Concerning the side effects and toxicity we can say that, compared to tricyclic antidepressants and monoamine oxidase inhibitors, SSRIs and SNRIs have real advantages including higher efficacy, improved tolerability and safety (Thase M.E., 2008; Shelton R.C., 2009).

Nontricyclic SNRIs have proved to be effective in major depressive disorder, generalized anxiety disorder, social phobia and panic disorder. In addition, all SNRIs seem to be helpful in neuropathic pain, fibromyalgia and chronic musculoskeletal pain, a property not characteristic to SSRIs and which is thought to be in relationship with their capacity to elevate the norepinephrine levels (Dobrescu D. et al., 2014; Sindrup S.H. et al., 2005).

SNRIs efficiency in the treatment of depressive disorders has been demonstrated in many studies. There are few studies reporting significant differences between SNRIs and SSRIs in moderate to severe depression treatment. As the first available SNRI, venlafaxine has been well studied and many of the earlier pooled or meta-analysis suggested that venlafaxine may have greater efficacy than SSRIs as a class. One notable limitation of these studies was the inclusion of only venlafaxine as SNRI and fluoxetine as SSRI, respectively. Anyway, at least these studies showed the superiority of venlafaxine in comparison with conventional SSRIs such as fluoxetine (Bradley A.J., Lenox-Smith A.J., 2013; Smith D. et al., 2002; Thase M.E. et al., 2007; Stahl S.M. et al., 2002).

Most current studies have shown that SNRIs (venlafaxine, duloxetine) are as effective or have a modest efficacy advantage compared to SSRIs in obsessive-compulsive disorder and major depressive disorder. In addition, SNRIs appeared better tolerated and have a rapid onset of antidepressant activity. Also SNRIs treatment resulted in higher remission rates and low overall dropout rates among patients than therapy with SSRIs suggesting that people who have failed to reach remission with an SSRI may benefit from treatment with an SNRI (fig. 1) (Dell'Osso B. et al., 2006; Papakostas G.I. et al., 2007; Bauer M. et al., 2009; Shelton C.R., 2009; Llorca P.M., Fernandez J.L., 2007).

Many of these studies did not include data on citalopram. Escitalopram, S-(+)-enantiomer of citalopram, is more potent as a serotonin reuptake inhibitor than its stereoisomer, R-(-)-citalopram. Due to its capacity to bind to the primary site as well as to a secondary site on the serotonin transporter, escitalopram has a superior efficacy in comparison with conventional SSRIs and comparable with that of venlafaxine. The advantages of escitalopram over venlafaxine consist in better efficacy and tolerability, excellent safety and higher remission rates (Llorca P.M., Fernandez J.L., 2007; Klein N. et al., 2004; Lam R.W. et al., 2010).

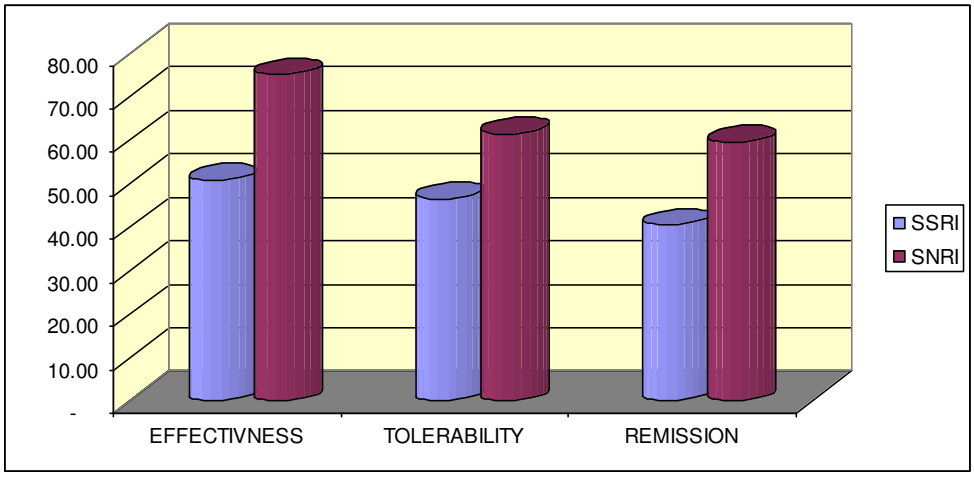

Fig. 1. Differences between SNRIs and SSRIs

In our study, we scanned the records concerning the pharmaceutical prescriptions for patients suffering from depression and undergoing a treatment with antidepressants. This study has evaluated four antidepressants: two SSRIs (citalopram, escitalopram) and two SNRIs (duloxetine, venlafaxine) as seven pharmaceutical products in a community pharmacy in Oradea city between 2008 and 2014 as can be seen in table 1 (Colopelnic N., 2015).

Table 1

SSRI and SNRI drugs used to treat depression

Item No.	International common name	Proprietary name	Dose	Pharmaceutical presentation
1.	**CITALOPRAM**	CITALOPRAM	5 mg; 10 mg	tablets
2.	**ESCITALOPRAM**	CIPRALEX	5 mg; 10 mg; 15 mg; 20 mg	tablets
		ESCITALOPRAM		
3.	**DULOXETINE**	CYMBALTA	30 mg; 60 mg	capsules
4.	**VENLAFAXINE**	EFECTIN EP	37.5 mg; 75mg; 150 mg	capsules
		FOBILESS		
		VELAXIN		

To estimate the exact amounts of antidepressants used in therapy, we followed the release of these drugs from pharmacy using their international common name and not proprietary name, avoiding a study based on a particular pharmaceutical product (table 2).

Table 2

The amounts of pharmaceuticals containing SSRI and SNRI drugs issued during the years 2008-2014

Item No.	International common name	Dose	2008/ boxes	2009/ boxes	2010/ boxes	2011/ boxes	2012/ boxes	2013/ boxes	2014/ boxes
1.	**Citalopram**	10 mg	1	3	2	2	1	0	0
2.	**Escitalopram**	10 mg	37	34	30	31	48	71	108
3.	**Duloxetine**	30 mg	0	0	0	0	8	8	10
		60 mg	0	1	0	0	0	0	2
4.	**Venlafaxine**	75 mg	40	43	17	13	30	29	35
		150 mg	0	0	0	4	5	9	10

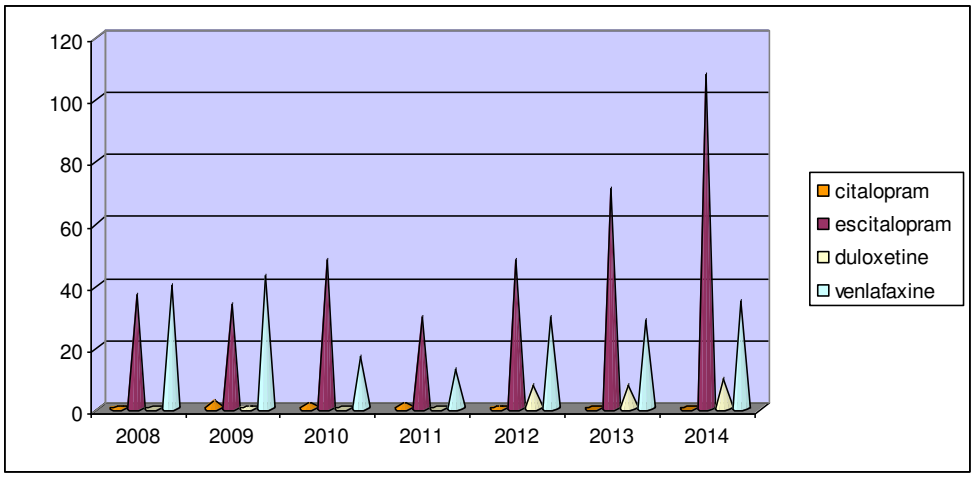

Fig. 2. The pharmaceuticals containing SSRIs and SNRIs issued during the years 2008-2014

The pharmaceutical market offers formulations containing both citalopram-racemate and enantiomer S form, respectively. As can be seen in table 2 and figure 2, escitalopram has a superior rate of use compared to citalopram. Considering the higher antidepressant effect and lower rate of adverse effects, it is easy to understand why escitalopram is more frequently prescribed to patients than the citalopram-racemate. Among the SNRIs, it can be seen a higher rate of use of venlafaxine compared to duloxetine which may be due to anxiolytic properties of venlafaxine. For this reason venlafaxine may be favored in the treatment of depression accompanied by anxiety disorder. Anyway, duloxetine brings major benefits in cases of major depression accompanied by somatic symptoms or in somatic

disorders such as fibromyalgia or peripheral neuropathic pain with or without depression. Comparing SNRIs and SSRIs during 2008-2009, it can be seen that venlafaxine and escitalopram showed a comparable therapeutic use in the studied area. Starting with 2010, the therapeutic benefits of escitalopram resulted in increased prescription rates and thus escitalopram's medical use in the therapy of depression surpassed venlafaxine in the studied area of Oradea city.

CONCLUSIONS

The study of SSRIs (citalopram, escitalopram) and SNRIs (duloxetine, venlafaxine) showed that the newer dual antidepressants with combined mechanism of action may be an important development in psycho pharmacology. Recent studies suggest that SNRIs are as effective or have a modest efficacy advantage compared to SSRIs in some depressive disorders. SNRIs have a rapid onset of antidepressant activity and SNRIs treatment frequently resulted in higher remission rates. In addition, the side effects of SNRIs are reported to be slightly less severe in comparison to the SSRIs.

An exception in the series of SSRIs is escitalopram, a substance with intense antidepressant effect and high tolerability. The literature published data and our study in a community pharmacy in Oradea city support that escitalopram has pharmacological advantages relative to the most frequently prescribed SNRI venlafaxine. The SNRIs are currently among the most widely used antidepressants, behind the SSRI escitalopram. The SNRIs are used as second-step treatment being prescribed by doctors to patients suffering of depression resistant to other drugs or recurrent depressive episodes.

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