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Are dual action antidepressants superior than selective antidepressants? Part I

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Summary

Depression is a complex disease with some psychiatric comorbidities, especially anxiety disorders and some comorbid physical symptoms.During the past few years, there has been a strong interest in the development of dual-action antidepressants with a better side effect profile. There are interesting pharmacological reasons why an antidepressant that act on more that one neurotransmitter system might have superior efficacy than antidepressant with single action. There also is an increasing body of evidence for an efficacy advantage in some patients with selective dual-action antidepressants, especially in large group of patients with high manifestation of physical symptoms of depression. Dual-acting antidepressants that inhibit reuptake of both serotonin and norepinephrine (SNRIs) treat a wider array of depressive symptoms (psychological and physical) than antidepressants that target either neurotransmitter alone. SNRIs such as venlafaxine, and duloxetine, may have an earlier onset of action, superior remission abilities, and better efficacy in treating anxiety symptoms of depression than the SSRIs. The remission rates of the patients taking venlafaxine were significantly higher than those of the patients taking SSRIs, regardless of age or gender. Overall, dual-acting agents appear to be more effective than single-acting agents in improving mood, reducing pain, and increasing the chance of remission.

Key words: antidepressants – SNRIs - SSRIs– treatment guidelines

Over the last decade, selective serotonin reuptake inhibitors (SSRIs) have become the most widely used class of antidepressants. Because the SSRIs act mainly on a single neurochemical, serotonin, they are single-action antidepressants. SSRIs have enjoyed acceptance among clinicians and patients mainly because of a better side effect profile than the medications that were popular previously, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). The SSRIs were developed in an attempt to produce medications that caused fewer intolerable side effects by refining the mechanism of action while maintaining antidepressant efficacy. Recently, some concerns have been raised that the single-action SSRIs may be less effective than the dual action TCAs and MAOIs. The SSRIs may have a slower onset of action, lower remission rates, and less efficacy in controlling the physical symptoms of depression than dual-action antidepressants. During the past few years, there has been a strong interest in the development of dual-action antidepressants with a better side effect profile.

Depression is a very complex disease with large set of symptoms that minority of them is serotonin dependent. Diagnostic criteria of major depression by DSM-IV are at least one of the following two abnormal moods which significantly interfered with the person's life: (1) abnormal depressed mood most of the day, nearly every day, for at least 2 weeks, and/or (2) abnormal lost of all interest and pleasure most of the day, nearly every day, for at least 2 weeks [1]. Additionally minor symptoms of depression involve both psychological (e.g., disturbances in sleep, appetite, weight, energy, and psychomotor activity) and physical symptoms (e.g., apathy, morbid preoccupation with worthlessness, suicidal ideation, or psychotic symptoms). It means that depression is a complex mental disorder with dual symptoms and should be also treated in a complex way.

Mechanisms of antidepressants action

All antidepressants have similar but no equal efficacy, and different effectiveness. Many medications are available for the treatment of major depression. Antidepressants are effective treatment for 65-75% of all patients with depression.The initial choice of an antidepressant is empiric and is typically based on the patient's prior history of response, family history of response, concomitant disease states, adverse-effect profiles, potential for drug interactions with other medications, and cost. An adequate therapeutic trial for an antidepressant is generally giving the agent at adequate doses continuously for 4-6 weeks [2]. The last decade has seen a considerable decline in the use of tricyclic antidepressants

(TCAs) with non-selective mechanisms of action and the emergence of new, more selective antidepressants, particularly those with more than one action on receptors or monoamines of interest – serotonin (SSRI), noradrenaline (SNRI+NARI) and dopamine (NDRI) – as well as noradrenaline and selective serotonin agonists (NaSSA) and reversible inhibitors of monoamine oxidase A (RIMA) [2].

There are seven major mechanisms of action for the antidepressants that are currently available. The mechanisms of action of older antidepressants (TCAs and MAOIs) are well known. The actions of newer antidepressants include: selective serotonin re-uptake inhibition (SSRIs); dual serotonergic and noradrenergic re-uptake inhibition (SNRI); dual noradrenergic and dopaminergic inhibition ; selective noradrenergic re-uptake inhibition (NRI); reversible inhibition of monoamine oxidase (RIMA); a re-uptake inhibition plus action at serotonin receptors; action at both noradrenergic and serotonergic receptors [2]. There are interesting pharmacological reasons why an antidepressant that act on more that one neurotransmitter system might have superior efficacy than antidepressant with single action. Although increasing actions of either noradrenaline or serotonine is an effective way to treat depression, there is some evidence that these two neurotransmitter systems have rather different effects on the various psychological (apathy, morbid preoccupation with worthlessness, suicidal ideation, or psychotic symptoms) and physical (disturbances in sleep, appetite, weight, energy, and psychomotor activity) functions that are disrupted in depression. There is considerable overlap between neurotransmitters and symptoms of depression, and some symptoms are more relevant to either serotonine, noradrenaline or dopamine. So serotonine-enhancing drugs might be preferred in patients with prominent anxiety symptoms (e.g. obsessions, social phobia or panic attack) whereas more noradrenaline-targeting drugs would be preferred in subjects who are lacking energy, attention or drive. Dual action antidepressants would be effective across more than one action drugs [2,3,4]. In recent years the potential advantages of dual serotonine and noradrenaline reuptake blockers are compared with SSRIs [5,6]. In one study clomipramine (TCA with high serotonine reuptake) showed superior efficacy than different drugs from SSRIs (paroxetine, citalopram), which was related to noradrenaline reuptake blocking properties of metabolite of clomipramine as well as the 5HT-blocking properties of the parent compound.

Efficacy and effectiveness of antidepressants

As it was mentioned above in recent years the potential advantages of dual action serotonine and noradrenaline reuptake blockade compared with either alone have been reported. Dual-action antidepressants may be especially more effective than single-action antidepressants in treating the somatic symptoms that frequently occur in depression [5]. The dual-action TCAs and MAOIs are more effective for the painful physical symptoms associated with depression than the SSRIs, but their side effects make them less tolerable [2]. There also is an increasing body of evidence for an efficacy advantage in some patients with selective dual-action antidepressants, especially in large group of patients with high manifestation of physical symptoms of depression [7,8]. A growing literature explores the mind-body connection in mental illness. Depression may have physical causes and consequences (like appetite and sleep disturbance, fatigue, and chronic pain). The presence of physical symptoms in depression may affect response to treatment. Both serotonin and norepinephrine systems are part of the body's endogenous analgesic system and they play overlapping but divergent roles in depression, and are involved in the etiology of some physical and emotional symptoms of depression [7,8]. Serotonin-norepinephrine reuptake inhibitors (SNRIs), but no SSRIs, venlafaxine and duloxetine have reduced pain sensitivity in a dose-dependent manner in patients with diabetic neuropathy [9]. Venlafaxine (at higher doses) and duloxetine may be especially efficacious in alleviating physical, anxious, and negative mood symptoms of depression [6]. Dual-acting agents that modulate serotonin and norepinephrine are more effective than single-acting agents in treating the emotional and physical symptoms of depression, including pain, especially in women of perimenopausal age [2,6]. Combination of fluoxetine (serotonergic action) and desipramine (noradrenergic action) was more effective in treating depression than either agent alone [10].Dual-acting TCAs were more effective in many studies in treating depression than TCAs or selective serotonin reuptake inhibitors (SSRIs) [2]TCAs have also a considerable side effect profile, can be lethal in overdose. Response to antidepressant treatment frequently falls short of remission [2]. Full remission is achieved more readily when the entire spectrum of depressive symptoms is targeted: (a) with medication (single-acting vs. dual-acting agents), and/or (b) with psychotherapy.Thase et al. published a pooled analysis of

8 studies comparing venlafaxine and various SSRIs, including fluoxetine and paroxetine. The authors found that the SSRIs needed 4 weeks to separate from placebo in rates of remission (a score of ≤ 7 on the HAM-D) but venlafaxine needed only 2 weeks to do the same. Also, venlafaxine was superior to the SSRIs in the final remission rate achieved. In this pooled analysis, the remission rate for patients taking placebo was 25%, the remission rate for patients taking an SSRI was 35%, and the remission rate for patients taking venlafaxine was 45% [6]. A follow-up study by Entsuah et al. [11] examined the studies included in the analysis by Thase et al. and found no significant age-by-treatment, gender-by-treatment. The remission rates of the patients taking venlafaxine were significantly higher than those of the patients taking SSRIs, regardless of age or gender. In contrast to SSRIs, which have shown a flat dose–response curve, venlafaxine showed increased efficacy (percentage of patients achieving remission) with increased dosages in this placebo-controlled dose–ranging study. Venlafaxine has the largest database of comparative trials and shows superior efficacy compared with a number of SSRIs across the spectrum of depressed patients, from primary care through to out-patients and those in hospital. Response to antidepressant treatment frequently falls short of remission. Venlafaxine has not only demonstrated a superior response, but also superior remission rates compared with the SSRIs fluoxetine, sertraline and paroxetine [6]. Overall, dual-acting agents appear to be more effective than single-acting agents in improving mood, reducing pain, and increasing the chance of remission [12].

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