

## Contemporary approach to pharmacological and clinical aspects of novel antidepressants

Vita Danilevičiūtė, Audrius Sveikata<sup>1</sup>

Clinic of Psychiatry, Vilnius University, State Center of Mental Health, Lithuania,

<sup>1</sup>Department of Basic and Clinical Pharmacology, Kaunas University of Medicine, Lithuania

**Key words:** depression, antidepressants, classification, mechanism of action.

**Summary.** Depression is the most common illness that affects a large number of individuals in all countries. Recent evidence suggest that depressive episodes if left untreated may heighten severity of subsequent episodes and may increase need for more health care resources.

The first antidepressants, tricyclics and monoamine oxidase inhibitors, became available in the late 1950s. A progressive tightening of requirements by drug licensing authorities has ensured that efficacy evidence is good for most antidepressants that are in use.

Contemporary antidepressant classification system is based on the mechanism of action, which is presumed to be responsible for their antidepressant effects. A pharmacodynamic system of classification has advantages because it incorporates the current theories of disease pathophysiology. Understanding the basic aspects of mechanism of action of antidepressants is important for treatment of depressive episode, for development of augmenting strategies and combining antidepressants with other antidepressants or antipsychotics.

Antidepressants as a class of psychotropic medication have the broad range of indications. The choice of initial antidepressant legitimately varies considerably among clinicians and countries. Referring to some differences of recommendations for the first line treatment of depressive episode we suppose that the choice of antidepressant medication must be individualized for a particular patient. Novel antidepressants (SSRI, SNRI, NaSSA, NARI, NDRI and other) are safe and better tolerated. Metabolism of novel antidepressants is much improved compared with MAOIs and TCAs.

The combination of antidepressants is an important clinical issue. There are the following principles of combining antidepressants: 1. to combine mechanisms of action not just drugs, 2. to combine antidepressants and to promote pharmacological synergy and tolerability, 3. to use important synergies within the serotonin, noradrenaline and even dopamine monoaminergic systems.

Adequate treatment of depression including modern treatment approaches has the potential to reduce suffering and disability substantially and minimise the risk of suicide.

### Introduction

Depression is a most common illness that affects a large number of individuals in all countries. However, depression is underdiagnosed and frequently undertreated. Recent evidence suggests that depressive episodes, if left untreated, may heighten severity of subsequent episodes and may increase need for more health care resources. The importance of depression as a major public health problem is emphasized by finding its place in the range of global burden of diseases. Depression was the fourth largest cause of burden of disease worldwide in 1990,

and by 2020 it is expected to be the second largest cause of burden of disease (1). Over 10% of the population will have depression within their lifetime. The range of lifetime risk for major depressive disorder in community samples is from 10% to 25% for women and from 5% to 12% for men. The range of point prevalence of major depressive disorder in community samples is from 5% to 9% for women and 2% to 3% for men (2). Some individuals have only a single episode with full return to premorbid functioning, however, 50% to 85% have recurrence of depression.

The history of antidepressant pharmacotherapy begins with the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)(3). Both of these classes of antidepressants were successful and were discovered by chance. The first antidepressants, tricyclic and monoamine oxidase inhibitors, became available in the late 1950s. A progressive tightening of requirements by drug licensing authorities has ensured that efficacy evidence is good for most antidepressants that are in use.

### Classification of antidepressants

Contemporary antidepressant classification system based on the mechanism of action presumed to be responsible for their antidepressant effects eliminates the confusion around significance of the structure. A pharmacodynamic system of classification has advantages, because it incorporates the current theories of disease pathophysiology. This system can easily accommodate new agents as they become available because it is based on the established pharmacology of drugs. Many of references using a functional classification system, classify currently available antidepressant drugs into the following classes (4- 8):

1. Non-selective antidepressants:
  - 1.1. Serotonin and noradrenalin reuptake inhibition with effects on multiple receptor system and sodium conductance (TCAs),
  - 1.2. Monoamine oxidase inhibitors (MAOI),
2. Selective reuptake inhibitors:
  - 2.1. Selective serotonin reuptake inhibitors (SSRI): citalopram, escitalopram (9, 10), fluoxetine, fluvoxamine, paroxetine, sertraline,
  - 2.2. Selective noradrenaline reuptake inhibitors (NARI): reboxetine,
  - 2.3. Serotonin and noradrenalin reuptake inhibitors (SNRI): venlafaxine, milnacipran,
  - 2.4. Noradrenalin and dopamine reuptake inhibition (NDRI): bupropion
3. Receptor blockers
  - 3.1. Serotonin (5-HT<sub>2A</sub> and 2C, 5-HT<sub>3</sub>) receptor blockade with noradrenalin (alpha-2) receptor blockade - noradrenergic and specific serotonergic antidepressant (NaSSA): mirtazapine,
  - 3.2. Serotonin (5-HT<sub>2A</sub>) receptor blockade with serotonin reuptake inhibition: nefazodone,
4. Others

Tianeptine - the drug that has been found to be an effective antidepressant. Tianeptine actually increases the uptake of serotonin into nerve endings, an effect that is opposite to the standard selective

serotonin inhibitors. Tianeptine decreases both serotonin transporter mRNA and that of binding sites (11).

In the Clinical Guidelines for the Treatment of Depressive Episode elaborated by Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT) antidepressants are divided into three major classes (12):

1. TCAs and MAOIs,
2. SSRIs,
3. Novel antidepressants: including NDRI (bupropion\*), NaSSA (mirtazapine), NARI (reboxetine), SNRI (venlafaxine), nefazodone and moclobemide (reversible inhibitor of MAO A - RIMA)

\*Bupropion is one of the oldest of the newer antidepressants, which entered clinical trials in the mid-1970' and was approved before fluoxetine. Marketing of bupropion was delayed after its approval because of the risk of seizures (3). After extensive clinical investigations bupropion was released again for clinical use.

General biological studies of depression have highlighted the role of neurotransmitters in the treatment of depression. The mechanisms of action of antidepressants are not well known and we are still on a long way from understanding the critical connections and cellular interaction during depressive episode. However, understanding the basic aspects of mechanism of action of antidepressants is important for treatment of depressive episode, for development of augmenting strategies and combining antidepressants with other antidepressants or antipsychotics.

### Indications of antidepressants

Antidepressants as a class of psychotropic medication have the following broad range of indications (3):

*Diagnostic indications for antidepressants:*

1. Mood disorders: major depressive disorder, bipolar disorder, cyclothymic disorder, dysthymic disorder,
2. Psychotic disorders,
3. Substance-induced mood disorders.

*Indication for antidepressants: other psychiatric and medical condition:*

1. Sleep disorders,
2. Anxiety disorders,
3. Eating disorders,
4. Substance related disorders
5. Others: pain syndromes, irritable bowel syndrome, enuresis, arrhythmias and some immune dysfunction.

### **Some aspects of clinical pharmacology of antidepressants**

The goals of treatment of affective disorders are to alleviate acute symptoms, to restore psychosocial functioning, and to prevent relapse and recurrence. Important decisions in clinical management are the appropriate selection of an intervention and treatment setting. Clinical decisions regarding management usually focus on four key issues:

1. The severity of the disorder (including risk of harm to self or others),
2. The availability of effective treatments (either specific antidepressants or trained therapists),
3. Patient's preference, and
4. The nature of any associated difficulties.

When choosing the antidepressant the important aspects are: 1) safety, including possibility of overdosing or pregnancy, 2) previous response by patient or family member, 3) symptom profile or type of depression (anxious or retarded), 4) side effect profile, 5) concurrent medication, 6) other medical illness, 7) age of patient, 8) patient's compliance, 9) physician's experience with antidepressant.

The most important indications for use of medication are probably severity and persistence of depression. Impairment of function and suicidal ideation in the context of the depressive syndrome are the other indications to treat with antidepressants. For moderate or severe depressive episode antidepressants should be used irrespective of life stress or symptom pattern: counseling and psychotherapy may be combined with antidepressants where indicated.

The choice of initial antidepressant legitimately varies considerably among clinicians and countries (13). Where cost is an important consideration, some older TCAs are in use because of the price. Where cost minimization is less crucial, SSRIs and novel antidepressants often have advantages in side effects and tolerability. Irrespective of the first choice, troublesome side effects indicate a change to an antidepressant with a different side-effect profile. Monoamine oxidase inhibitors are little used as the first choices. When there was a previous history of antidepressant response, the best first choice is the antidepressant to which the patient responded previously.

Canadian Psychiatric Association and CANMAT (12) recommend SSRIs and novel antidepressants: including NDRI (bupropion), NaSSA (mirtazapine), NARI (reboxetine), SNRI (venlafaxine), nefazodone and moclobemide as first-line treatment. Amitriptyline and clomipramine being second line treatment have greater efficacy than SSRIs in hospitalized patients with depression but safety and tolerability issues have

to be considered. Other TCAs and MAOIs are third line treatment.

Janicak et al. (3) recommend venlafaxine, nefazodone, mirtazapine (if expense is not an issue) or previously effective antidepressant as the first line treatment for major depressive episode without psychotic features SSRIs. If the price is an issue, the choice for treatment are TCAs, if side effects are tolerated; preferably using a secondary amine TCA.

Schaztzberg et al. (11) emphasize that the initial evaluation of patients presenting with depressive symptoms should include careful medical examination and clinicians must consider the possible physical illness. The choice for antidepressant depends of side effects profile and physical condition.

Davis et al. (6) emphasize that all antidepressants have established efficacy in major depressive disorder. However, other parameters such as safety in overdose, long-term tolerability and the potential for drug-drug interactions or likelihood of remission play major role in selecting the first antidepressant.

Stahl (14) recommends as the first line monotherapy the following antidepressants: SSRIs, bupropion, venlafaxine, mirtazapine, nefazodone, and reboxetine. The second line monotherapy for depressive episode could be TCAs and MOAIs.

Shiloh et al. (15) recommend as the first line treatment SSRIs, TCAs and novel antidepressants (venlafaxine, bupropion, nefazodone, mirtazapine, reboxetine). However, TCAs should not be used if patient is suicidal. Referring in some differences of recommendations for the first line treatment of depressive episode we suppose that the choice of antidepressant medication must be individualized for a particular patient.

### **Choosing of antidepressant according their features**

The first classification system presented in this paper will be used during discussion on choosing of antidepressants.

#### ***Selective Serotonin Reuptake Inhibitors***

Selective serotonin reuptake inhibitors are so called, because they selectively inhibit the reuptake of serotonin from the synaptic gap. The simplified concept of selective serotonin reuptake inhibitors is usually used to describe how these agents work but it does not describe important features of the group as a whole and of the individual agents. An important consequence of increasing serotonin is the stimulation of post-synaptic serotonergic receptors. There are many subtypes of serotonergic receptors. There is an opinion that stimulation of serotonin 2C receptors

in the CNS is responsible for the increase of anxiety that is often associated with early stages of SSRIs therapy. Stimulation of serotonin 3 and 4 receptors in the gut is thought to account for the nausea and gastrointestinal upset that may occur in the first few days or weeks.

There are real differences among SSRIs for many individual patients, and sometimes only empirical trial will lead to the best choice of SSRI to an individual patient. Differences among the individual SSRIs in terms of their therapeutic effect and side effects may be at least partly attributable to differences in their secondary binding properties.

Relatively the most selective SSRIs escitalopram (9,16) and citalopram (14) in general have no significant secondary pharmacological activities.

Fluoxetine has significant activity at serotonin 2C receptors, and serotonin 2C receptors are presumed to be involved in the regulation of appetite and food intake. The affinity for serotonin 2C receptors might explain why fluoxetine is also the SSRI that gained approval for eating disorders. Blockade of the serotonin 2C receptors may be involved in the alleviation of psychosis. (8). Fluoxetine has some activity with noradrenaline reuptake inhibition as well (15). Fluoxetine also binds to cytochrome P450 3A4 and 2D6, this is important for drug interaction (TCAs and others).

Paroxetine is the only SSRI with significant binding at muscarinic receptors for acetylcholine (14). It might imply greater incidence of anticholinergic side effects, possibly increased sedation and cognitive impairment. Paroxetine inhibits nitric oxide synthase. This might explain why paroxetine tends to be most associated with erectile dysfunction. Paroxetine also inhibits the reuptake of noradrenaline to some extent. Paroxetine binds to cytochrome P450 2D6, and this important for interaction with TCAs and other drugs. Paroxetine has more expressed discontinuation effects.

Sertraline is the only SSRI with a significant effect on the reuptake of dopamine and this may explain why it is the only of these drugs that does not raise the serum levels of the hormone prolactin. The influence of sertraline on dopamine reuptake inhibition may be problematic in psychotic depression (17). The influence of sertraline on dopamine reuptake could precipitate or aggravate psychotic symptoms (8).

All the SSRIs (except fluoxetine) have half-lives of 15-30 hours. Fluoxetine and its active metabolite, norfluoxetine, have half-lives of 2 to 4 and 7 to 15 days, respectively. For all of these reasons, fluoxetine should be reserved for cases in which the advantages of its long half-life outweigh its disadvantages.

Fluvoxamine, fluoxetine and paroxetine have nonlinear pharmacokinetics, which means that dose increases lead to disproportionately greater increase in plasma drug levels. Escitalopram, citalopram and sertraline have linear pharmacokinetics (3). Dose increase with fluvoxamine, fluoxetine and paroxetine can lead to greater increases of serotonin mediated adverse effects and inhibition of specific cytochrome P450 enzymes. (3, 8).

The basic data on pharmacokinetics and dosing of SSRIs are presented in Table.

#### **Selective noradrenaline reuptake inhibitor**

Some TCAs (e.g., desipramine, nortriptyline) block noradrenaline reuptake more potently than serotonin reuptake. These TCAs are not really selective noradrenaline reuptake blockers since they block other receptors as well. The first really selective noradrenergic reuptake inhibitor (NARI) is reboxetine. Thus, reboxetine is a pharmacological complement to the SSRIs since it provides selective reuptake inhibition greater than serotonin reuptake inhibition. Reboxetine does not inhibit electrically excitable membranes and for this reason overdose of reboxetine should not cause significant risk of cardiotoxicity or seizures (3,18). Reboxetine has linear pharmacokinetics over its clinically relevant dosing range and half-life of approximately 12-16 hours (3, 8). Due to its short half-life (approximately 12 or more hours) the daily dose must be divided. The daily dose of reboxetine ranges from 4mg to 10 mg daily (in divided dose). In all studies reboxetine had similar time (2 to 3 weeks) to onset of the antidepressant efficacy, as do other antidepressants with usual onset of action. Reboxetine was shown to have good impact on social adaptation. The Social Adaptation Self-evaluation Scale (SASS) was used to evaluate patients' social motivation and behavior in depression. There was more pronounced improvement in SASS total score in patients treated with reboxetine compared with those on fluoxetine (19). The efficacy of reboxetine in anxiety and panic, not predicted from the known psychopharmacology of noradrenaline suggests a role for the noradrenaline pathway in anxiety and panic. (20). Adverse events, which have been more frequently observed in reboxetine versus placebo-treated patients, were dry mouth, constipation, insomnia, increased sweating, tachycardia, vertigo urinary hesitancy and/or retention (18). Reboxetine is basically metabolized by CYP 3A3/4 and this dose should be reduced when used in combination with drugs that are substantial inhibitors of CYP .

#### **Serotonin and noradrenalin reuptake inhibitors**

There is opinion based on trials and clinical practice that neither all patients with depression respond to



**Table. Pharmacokinetics and dosing of serotonin reuptake inhibitors (SSRIs) and novel antidepressants\***

Medication	Usual effective dosing (mg daily)	Range (mg daily)	Biotransformation pathways	Half-life	Protein binding
SSRI: Citalopram	20–40	10–60	Demethylaton in 2 steps involves CYP2C19, 206 and 3A4	37 hrs	80%
Fluoxetine	20–40	10–80	Demethylaton involves CYP2D6	4–6 days	95%
Fluvoxamine	100–200	50–300	Demethylaton ir deamination involves CYP2D6 and 1A2	7–22 hrs	80%
Paroxetine	20–40	10–60	Oxidation and demethylaton involves CYP2D6	24 hrs	95%
Sertraline	50–100	50–200	Demethylaton involves CYP3A4	25–26 hrs	98%
Novel: Bupropion SR	150–300	150–300 (divided dose)	Hydroxylation involves CYP2B6	21 hrs	84% (parent)
Mirtazapine	15–45	15–45 (single dozè)	Demethylaton and hydroxylation involves CYP2D6, 1A2 and 3A4	20–40 hrs	85% (parent)
Milnaciprane	15–150	50–200 (divided dose)	Glucoronisation	8 hrs	13%
Nefazodone	300–500	300–500 (divided dose)	Dealkylation and hydroxylation involves CYP3A4 and 2D6	1,5–4 hrs (parent) HO-Hef 18–33 hrs (TAD)	99% (parent)
Reboxetine	4–8	4–10 (divided dose)	Dealkylation and hydroxylation involves CYP3A4	13 hrs	97% (parent) a-I-acid glycoprotein > albumin
Venlafaksine IR/XR	75–225	37,5–375	O-demethylaton involves CYP2D6 and others.	5–7 hrs (ODV) and 11–13 hrs (ODV)	27% (parent) and 30% (ODV)

\*Adapted from Canadian Pharmaceutical Association, 2001.

SSRIs nor do all respond to NARI. Moreover, many patients who respond to SSRIs, do not remit completely and seem to have improved mood with noradrenergic deficiency syndrome, which sometimes is called apathetic response to SSRIs (14).

Venlafaxine is the new drug in this group, which inhibits first serotonin reuptake and later venlafaxine inhibits noradrenaline reuptake as well. High doses of venlafaxine have some activity at dopamine reuptake inhibition. Venlafaxine and its active metabolite O-desmenthylvenlafaxine (ODV) bind to plasma protein, 27% and 30% respectively. Venlafaxine and ODV have approximate half-lives of 5 and 11 hours, respectively. At the doses less than 150mg/day it is potent blocker of serotonin reuptake as imipramine but is weak blocker for noradrenalin reuptake (17).

Venlafaxine with doses less than 150mg/day basically is selective serotonin reuptake inhibitor - SSRI. Venlafaxine has a low binding for other receptors and does not inhibit Na<sup>+</sup> ion fast channels, making it relatively safe in overdoses compared with TCAs (21). Venlafaxine is available in immediate release (IR) and extended release (XR) formulations. Venlafaxine IR doses range from 75mg to 375mg/day in divided doses. The extended release formulation venlafaxine XR can be dosed once daily in the morning or evening. The administration of high-dose venlafaxine produces a more rapid beta-adrenergic receptor subsensitivity and it could demonstrate more rapid antidepressant action. Remission rates of patients treated with venlafaxine had greater chance than those treated with SSRIs. Also there is opinion that doses of venlafaxine must

be more than 150 mg/day to maximize the likelihood of remission (22). Basically venlafaxine is safe and efficacious antidepressant (21, 23). The most common side effects are nausea, insomnia, somnolence, dizziness, dry mouth, headaches, constipation, asthenia, nervousness and increased perspiration. Sexual dysfunction has been reported with up to 12% abnormal ejaculation, 6% impotence, 2% anorgasmia. Because of short half-life of venlafaxine, rapid discontinuation has been associated with severe discontinuation effects. FDA recommendations on March 3, 2000 request to taper venlafaxine referring on the dose, duration of therapy, and the individual patient's needs. Patients who have received venlafaxine (effexor) for 6 weeks or more should have their dose tapered over at least a 2-week period. The use of higher doses of venlafaxine necessitates monitoring of blood pressure, as rates of sustained blood pressure elevation can exceed 10% during therapy above 300mg /day. Feigner reported that venlafaxine has raise diastolic blood pressure in about 5%-13% of patients when used in doses greater than 200-225mg/day, but in patients with pre-existing propensity for hypertension pressor effects may occur at lower doses (21). The blood pressure monitoring is recommended for all patients taking venlafaxine. Venlafaxine is dependent on CYP 2D6 and 3A3/4 enzymes for its biotransformation. A substantial inhibition of CYP 3A3/4 could result in a meaningful increase in both venlafaxine and ODV levels.

#### **Milnacipran**

Milnacipran blocks noradrenalin and serotonin reuptakes sites. Milnacipran is more potent inhibiting noradrenaline reuptake than serotonin reuptake. No postsynaptic receptor activity has been demonstrated by milnacipran (24, 25). The variation in plasma levels between patients is low. No active metabolites have been found in humans.

Milnacipran have been compared with some TCAs (amitriptyline, imipramine, clomipramine) and some SSRIs (fluoxetine and fluvoxamine). In general it was of equal antidepressant activity. (25) Mean protein binding of milnacipran is 13%. Its half-life is 8 hours. Milnacipran has a high bioavailability, low plasma protein binding and it is largely eliminated in the urine as parent compound or as a glucuronide (26, 27). These features suggest, that the likelihood of interactions with other drugs given concurrently is lower. Its dose range is 50-200mg /day in divided doses. Milnacipran was better tolerated than comparators. The general and cardiovascular tolerability of milnacipran are superior to TCAs. The tolerability of milnacipran was comparable with that

of SSRIs with a higher incidence of dysuria (24). Milnacipran was associated with higher incidence of headache, vertigo, sweating, anxiety, hot flushes and dysuria.

#### **Noradrenalin and dopamine reuptake inhibition**

Bupropion is a relatively weak inhibitor of dopamine reuptake, with modest effects on noradrenaline reuptake and no effects on serotonin reuptake. It does not appear to be associated with downregulation of postsynaptic beta-adrenergic receptors. However, presumed mechanism of action of bupropion is based on inhibition of reuptake of dopamine and noradrenaline. Its weak affinity for these reuptake pumps has raised questions whether these mechanisms are relevant to its antidepressant activity. The combined plasma concentration of bupropion and its three active metabolites (hydroxybupropion, threohydrobupropion, erythrohydrobupropion) is responsible for the inhibition of both these pumps. The combined level of bupropion and its active metabolites are in microgram per milliliter range versus nanogram per milliliter range for almost all other antidepressants. The high level of bupropion and its metabolites achieved on usual therapeutic doses may also account for its narrow therapeutic index in term of causing seizures (3, 28). Bupropion is rapidly absorbed. The elimination is biphasic (with an initial phase of approximately 1.5 hours and a second phase about 14 hours. (11). The sustained-release formulation of bupropion is bioequivalent to the immediate-release formulation. Mean protein binding of bupropion is 85%. Bupropion appears to be pharmacologically unique relative to other conventional antidepressants and mostly resembles the action of psychostimulants. Dosing of bupropion should begin in healthy adult 100mg twice a day and may be increased to 100mg thrice day after minimum of three days. An increase in dosage up to total 450mg day in divided doses that nor exceed 150mg each. The dosage of sustained release formulation is 300mg /day given 150mg twice a day. It is recommended to begin from 150mg once a day in the morning of sustained release-formulation. If it is well tolerated the 150mg twice a day can be administered at fourth day. At least 8 hours should elapse between doses. Bupropion appears to be relatively free of adverse effects on sexual function (28). The main safety risk of bupropion in overdosing is a risk of seizures. Blockade of dopamine reuptake is related with antidepressant activity of bupropion. However, this property could cause psychomotor activation and precipitation or aggravation of psychosis, which has been seen with bupropion (8). Such psychotic symptoms as hallucinations and delusions can emerge in association with bupropion treatment.

Other side effects of bupropion are overstimulation, agitation, and nausea. Careful evaluation of risk factors (history of seizures, recent withdrawal from alcohol or anxiolytic drugs, concomitant therapy with drugs that lower the seizure threshold, history of organic brain disease or abnormal EEG), conservative dose titration and use of divided doses should minimize the risk for bupropion related seizures.

#### ***Noradrenergic and specific serotonergic antidepressant (NaSSA)***

The novel antidepressant mirtazapine has dual mode of action. It is a noradrenergic and specific serotonergic antidepressant that acts by antagonizing central alpha2-adrenergic auto and hetero receptors, as well as by blocking 5-HT<sub>2</sub> and 5HT<sub>3</sub> receptors. Mirtazapine enhances noradrenergic and serotonergic neurotransmission. Bioavailability of mirtazapine is approximately 50%. Peak plasma concentration is reached within 2 hours. The elimination half-life ranges from 20 to 40 hours. Mirtazapine has linear pharmacokinetics. It is approximately 85% bound to protein in plasma. The putative mechanism of action of mirtazapine is unique among currently available antidepressants. Blockade of presynaptic central alpha2-adrenergic autoreceptors leads to enhanced noradrenergic neurotransmission via increased noradrenergic cell firing and noradrenalin release. In return, noradrenalin stimulates alpha-1 adrenoreceptors on the cell bodies of serotonergic neurons, which lead to increased serotonin cell firing. Mirtazapine also blocks alpha-2-adrenergic heteroreceptors on the synaptic terminals of serotonin neurons, which lead to a further increase in serotonin release. The overall effect of these pharmacological actions is increased noradrenergic and 5HT<sub>1A</sub> activity. (29)

The onset of action of antidepressants is a very important issue. Due to unique mechanism of action, mirtazapine was studied by many researchers. The opinion that mirtazapine has faster onset of action than SSRIs is confirmed by several researchers (30-33). Significant differences were seen between mirtazapine and SSRIs after the first week of treatment. Mirtazapine being antagonist of alpha 2 adrenoreceptors does not enhance serotonergic neurotransmission directly but disinhibits noradrenergic activation of serotonergic neurons and thereby increases serotonergic neurotransmission by mechanism that does not require a time dependent desensitization of receptors. These neurobiological phenomena may underlie apparently faster onset of action of mirtazapine compared with the SSRIs. Fast onset of action ensures that use of benzodiazepines, as concomitant treatment is less frequent with

mirtazapine than SSRIs. Long-term use of benzodiazepines could be addictive (34). Also, mirtazapine was superior to amitriptyline for the long-term treatment (3).

Much attention has been paid to sexual dysfunction associated with SSRIs. A variety of strategies exist to manage antidepressant induced sexual dysfunction including waiting, reducing the antidepressant dose, use of drug holiday, use of adjunctive pharmacotherapy or switching antidepressants. In contrast to SSRIs, mirtazapine has no sexual side effects (35).

Mirtazapine has been proved effective in the treatment of patients who were resistant or intolerant to SSRIs. The switch of mirtazapine could be made immediately without necessity for a taper period. In a double blind study in patients who were resistant to SSRIs treatment with mirtazapine had a more rapid onset of action than sertraline. Mirtazapine has also been effective in elderly depressed patient and again showed faster onset of action than another SSRI paroxetine. (36) Mechanism of action of mirtazapine enables to combine mirtazapine with other newer antidepressants, which are reuptake blockers (14). In one double-blind study (29) mirtazapine and paroxetine were equally effective but the combination of both antidepressants had a more robust antidepressant effect. The following side effects may occur in association with mirtazapine: drowsiness, excessive sedation, dry mouth, increased appetite and weight gain. Usually these side effects are mild and transient. No significant cardiovascular or sexual side effects were associated with mirtazapine.

Hematological side effects are very rare. There are over 10 million patients worldwide treated with mirtazapine and hematological side effects have been reported in few cases (29). Mirtazapine does not inhibit CYP 450 enzymes and therefore is not expected to interact with the metabolism of other drugs (8).

#### ***Serotonin (5-HT<sub>2A</sub>) receptor blockade with serotonin reuptake inhibition***

Nefazodone has selective and unique effects on the serotonin system. Nefazodone blocks serotonin reuptake, while functioning as a 5-HT<sub>2A</sub>-receptor antagonist. Nefazodone has some unusual pharmacological properties. Nefazodone is metabolized by CYP303/4 to form the active metabolite m-chlorophenylpiperazine (mCPP), which is a potent serotonin agonist. This metabolite is a 5HT-2C agonist and could paradoxically cause anxiety and stimulation instead of anxiety reduction and sedation. The elimination of mCCP is dependent of CYP 2D6.

Nefazodone is more specific in terms of affecting a subtype of serotonin receptors than the SSRIs or

venlafaxine (3, 6.) Nefazodone has bioavailability of 15-23% because of extensive first-pass hepatic metabolism. Nefazodone has nonlinear kinetics, which results in greater than proportional mean plasma concentration with higher doses. The elimination half-life is 2-4 hours for the parent compound. Nefazodone is extensively (about 99%) but loosely bound to proteins (11). Nefazodone is indicated for depression with anxiety, agitation, sleep disturbances, insomnia. Nefazodone is indicated for SSRIs induced sexual dysfunction, inability to tolerate SSRIs. Dose range is 300-500mg daily in divided doses. The most common side effects associated with nefazodone were dry mouth, somnolence, dizziness, nausea, constipation and blurred vision postural hypotension (8, 11). Nefazodone can potentiate the effects of other CNS depressants. The combination of nefazodone with other pro-serotonergic agents could result in development of the serotonin syndrome.

The main data about pharmacokinetics of all novel antidepressants are presented in Table.

### Strategies of clinical management of depressive disorders

There are three main options available to use for partial response or for treatment resistance cases:

1. Switch to another antidepressant,
2. Augment with another medication,
3. Use a combination of antidepressants,
4. Use a combination of antidepressants and antipsychotics.

Switching strategy for treatment resistant depression is usual in clinical practice. Switching to another antidepressant requires special care (37) including MAOIs, antidepressants with special tapering warnings (venlafaxine), and antidepressants of the same class. Basically switching is more clear strategy than augmentation or combination of drugs.

Faced with nonresponse to one or more trials of different antidepressants many psychiatrists try to combine antidepressants. Data supporting this approach is generally in short supply. Most physicians avoid combination with MAOIs due to very serious or even dangerous consequences of this combination.

There are some principles of combining antidepressants (14). The first principle is to combine mechanisms of action not just drugs. The second principle is to combine antidepressants and to promote pharmacological synergy and tolerability. The third principle of antidepressant combination is to use important synergies within the serotonin, noradrenaline and even dopamine monoaminergic systems. Lam et al. concludes that there is limited evidence supporting the

efficacy of combination of antidepressant treatment and recommend further studies for evaluation of combination of antidepressant strategy for treatment resistant depression. (38).

Due to unique mechanism of action, mirtazapine is interesting antidepressant for use in combinations with antidepressants or antipsychotics. Berk et al (39) report on 6-week randomized placebo-controlled trial of mirtazapine and haloperidol. The results of this study suggest a potential role of mirtazapine in the negative symptoms of schizophrenia. Carpenter et al. (40) referring on double-blind placebo controlled study of antidepressant augmentation with mirtazapine conclude that mirtazapine in combination with SSRIs (fluoxetine, fluvoxamine, citalopram, paroxetine, sertraline), bupropion and venlafaxine appears to be safe and effective for antidepressant combination in cases of partial response. Loonen (41) reports that risperidone and mirtazapine are effective and safe to use in combination. Shelton et al (42) hypothesized that fluoxetine could be augmented with olanzapine to treat resistant depression. An 8-week double blind study was conducted to treat patients with treatment resistant depression without psychotic features. Olanzapine and fluoxetine demonstrated superior efficacy for treating treatment resistant depression compared to either agent alone. Thase (43) reports that second generation antipsychotics are serotonin2A/2C antagonists, possibly all of them improve the efficacy and some of the side effect profile of SSRIs. In clinical trial the atypical antipsychotic olanzapine in combination with fluoxetine demonstrated clinical efficacy. Hirshfeld et al. (44) conclude that in treatment resistant depression boosting both serotonin and noradrenaline neurotransmission is important approach.

Sonawalla et al. (45) conclude that there is no specific treatment algorithm for severe depression. Also there is no specific treatment algorithm for treatment resistant depression. The conclusion is made that active use of antidepressants (at adequate doses for adequate duration) or antidepressant combination strategies are indicated.

### Conclusion

Since the introduction of novel antidepressants, therapeutic intervention when treating depression has broadened. Novel antidepressants are safe and better tolerated. Metabolism of novel antidepressants is much improved compared with MAOIs and TCAs. Adequate treatment of depression including modern treatment approaches has the potential to substantially reduce suffering and disability and minimize the risk of suicide.



## Šiuolaikinis požiūris į farmakologines ir kliniškes naujų antidepresantų savybes

Vita Danilevičiūtė, Audrius Sveikata<sup>1</sup>

Vilniaus universiteto Psichiatrijos klinika, Valstybinis psichikos sveikatos centras,

<sup>1</sup>Kauno medicinos universiteto Teorinės ir klinikinės farmakologijos katedra

**Raktažodžiai:** depresija, antidepresantai, klasifikacija, veikimo mechanizmas.

**Santrauka.** Depresija – tai dažna liga, kuria suserga didelis skaičius žmonių įvairiose pasaulio šalyse. Naujausi tyrinėjimų duomenys rodo, kad, negydant depresijos, vėliau gali kartotis sunkesni epizodai, kurių gydymui reikės didesnių kaštų. Pirmieji antidepresantai, tricikliai antidepresantai ir monoaminooksidazės inhibitoriai, klinikinėje praktikoje pradėti vartoti šeštojo dešimtmečio pabaigoje. Reikalavimai naujiems antidepresantams užregistruoti buvo nuolat griežtinami, ir tai užtikrino naujų dabar vartojamų antidepresantų kokybę. Šiuolaikinių antidepresantų klasifikacija pagrįsta veikimo mechanizmais, kurie nulemia antidepresinį poveikį. Farmakodinaminė klasifikacijos sistema turi pranašumų, kadangi apima pažangias depresijos patofiziologijos teorijas. Antidepresantų veikimo mechanizmo esminių aspektų supratimas yra svarbus gydant depresiją, sustiprinant antidepresantų veikimą kitais vaistais, derinant su kitais antidepresantais arba antipsichotikais. Antidepresantų, kaip psichotropinių vaistų grupės, indikacijos yra labai plačios. Antidepresantų pradinis parinkimas įvairiose šalyse skiriasi, taip pat skirtingai parenka juos ir gydytojai. Atsižvelgiant į tam tikrus skirtumus ir apibendrinant įvairių autorių rekomendacijas, kokie antidepresantai turėtų būti pirmojo pasirinkimo, galima padaryti išvadą, kad antidepresanto parinkimas kiekvienam pacientui turi būti individualus. Nauji antidepresantai (selektyvūs serotonino reabsorbcijos inhibitoriai, serotonino ir noradrenalino reabsorbcijos inhibitoriai, noadrenerginis ir specifinis serotonerginis antidepresantas, noradrenalino reabsorbcijos inhibitorius, noradrenalino ir dopamino reabsorbcijos inhibitorius ir kiti) yra saugūs ir gerai toleruojami. Naujų antidepresantų metabolizmas yra pranašesnis už monoamino oksidazės inhibitorių ar triciklių antidepresantų. Antidepresantų derinimas svarbus kliniškai. Pagrindiniai antidepresantų derinimo principai: 1) derinti ne tik vaistus, bet tinkamai derinti ir jų veikimo mechanizmus; 2) derinant didinti jų farmakologinį sinergizmą ir toleravimą; 3) atsižvelgti į jų farmakologinį sinergizmą serotonino, noradrenalino ir dopamino sistemoje. Veiksmingas depresijos gydymas, išnaudojant šiuolaikines gydymo galimybes, įgalina palengvinti sėganciuųjų būklę bei sumažinti savižudybės riziką.

Adresas susirašinėjimui: V. Danilevičiūtė, VU Psichiatrijos klinika, Vasaros 5, 2055 Vilnius  
El. paštas: [vita.dani@delfi.lt](mailto:vita.dani@delfi.lt)

### References

1. Lopez AD, Murray CJ. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990-2020 and projected to 2020. Boston, MA, Harvard University Press; 1996.
2. Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> ed., Text Revision (DSM-IV-TR), American Psychiatric Association; 2000.
3. Janicak PG, Davis JM, Preskorn SH, Ayd FJ. Principles and practice of Psychopharmacotherapy, 3<sup>rd</sup> ed., Lippincott Williams & Wilkins; 2001.
4. Beers MH, Berkow R, editors. The Merck Manual of Diagnosis and Therapy, 17<sup>th</sup> ed, Merck & Co., Inc.; 1999.
5. Kent JM. SNRIs, NaSSAs and NaRIs: new agents for the treatment of depression. Lancet 2000;355:911-8.
6. Davis KL, Charney D, Coyle JT, Nemeroff Ch, editors. Neuropsychopharmacology. The fifth generation of progress. Lippincott Williams&Wilkins; 2002.
7. Stahl SM. Psychopharmacology of Antidepressants, 2nd ed., Martin Dunitz; 1998.
8. Boer JA, Westenberg HGM, editors. Focus on psychiatry. Antidepressants: Selectivity or Multiplicity. Benecke N.I., Amsterdam, The Netherlands; 2001.
9. Baumann P, Zullino DF, Eap CB. Enantiomers' in psychopharmacology - a critical review with special emphasis on the antidepressant escitalopram. Eur Neuropsychopharmacol 2002;12:433-44.
10. Wade A, Lemming OM, Hedegaard KB. Escitalopram 10 mg is effective and well tolerated in a placebo controlled study in primary care. Int Clin Psychopharmacology 2002;17:95-102.
11. Schatzberg AF, Nemeroff ChB, editors. Essentials of Clinical Psychopharmacology. American Psychiatric Publishing; 2001.
12. Kennedy SH, Lam RW, Cohen NL, Ravindran AV, CANMAT Depression Work Group. Clinical guidelines for the treatment of depressive disorders. Medication and other biological treatments. The Canadian Journal of Psychiatry 2001;46(Suppl 1):38-58.
13. Gelder MG, Lopez Ibor Jr JJ, Andreasen NC, editors. New Oxford Textbook of Psychiatry, 1<sup>st</sup> ed., Oxford University Press; 2000.
14. Stahl SM. Essential Psychopharmacology, Neuroscientific Basis and Practical Applications, 2nd ed. Cambridge University Press; 2000.
15. Shiloh R, Nutt D, Weizman A. Atlas of psychiatric pharmacotherapy, revised ed. Martin Dunitz Ltd; 2000.
16. Owens MJ, Knight DL, Nemeroff CB. Second generation of SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. Biol Psychiatry 2001;50:345-50.
17. Gabbard GO, Editor-in-Chief, Treatments of Psychiatric Disorders. 3<sup>rd</sup> ed., American Psychiatry Press; 2001.
18. Mucci M. Reboxetine: a review of antidepressant tolerability.

- J Psychopharmacol 1997;11:33-7.
19. Massana J, Moller HJ, Burrows GD, Montenegro RM. Reboxetine: a double blind comparison with fluoxetine in major depressive disorder. *Int Clin Psychopharmacol* 1999; 14:73-80.
  20. Brunello N, Mendlewicz S, Kasper S, Leonard B, Montgomery S, Nelson JC, et al. The role for noradrenaline and selective noradrenaline reuptake inhibition in depression. *European Neuropsychopharmacology* 2002;12:461-75.
  21. Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: meta-analysis. *British Journal of Psychiatry* 2002;180:396-404.
  22. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *British Journal of Psychiatry* 2001;178:234-41.
  23. Feighner JP. Cardiovascular safety in depressed patients: focus on venlafaxine. *J Clin Psychiatry* 1995;56(12):574-9.
  24. Puech A, Montgomery SA, Prost JF, Solles A, Briley M. Milnacipran, a new serotonin and noradrenaline reuptake inhibitor: an overview of its antidepressant activity and clinical tolerability. *Int Clin Psychopharmacol* 1997;12:99-108.
  25. Spencer CM, Wilde MI. Milnacipran. A review of its use in depression. *Drugs* 1998;56:405-27.
  26. Puozzo C, Leonard BE. Pharmacokinetics of milnacipran in comparison with other antidepressants. *Int Clin Pharmacol* 1996;11(Suppl 4):15-27.
  27. Puozzo C, Panconi E, Deprez D. Pharmacology and pharmacokinetics of milnacipran. *Int Clin Psychopharmacol* 2002;17(Suppl 1):25-35.
  28. Preskorn SH. *Outpatient Management of Depression: a Guide for the Primary Care Practitioner*. 2<sup>nd</sup> ed., Professional Communications, nc.; 1999.
  29. Sami AK, Leinonen EVJ. A Review of the Pharmacological and Clinical Profile of Mirtazapine. *CNS Drug Reviewers* 2001;7:249-64.
  30. Quitkin FM, Taylor BP, Kremer Ch. Does Mirtazapine Have a More Rapid Onset Than SSRIs? *J Clin Psychiatry* 2001; 62:5:358-61.
  31. Stahl SM, Nierenberg AA, Gorman JM. Evidence of early onset of antidepressant effect on randomised controlled trials. *J Clin Psychiatry* 2001;62(Suppl 4):17-23:discussion 37-40.
  32. Blier P. Pharmacology of rapid-onset antidepressant treatment strategies. *J Clin Psychiatry* 2001;62(Suppl 15):12-7.
  33. Thompson C. Onset of action of antidepressants: results of different analysis. *Hum Psychopharmacol* 2002;17(Suppl 1):27-32.
  34. Danilevičiūtė V. *Benozodiazepinai. (Benzodiazepines.)* Vilniaus universiteto leidykla; 1998.
  35. Hirschfeld RM. Management of sexual side effects of antidepressant therapy. *J Clin Psychiatry* 1999;60(Suppl 14):27-30.
  36. Hirschfeld RM. The use of mirtazapine in difficult-to-treat patient populations. *Hum Psychopharmacol* 2002;17(Suppl 1):33-6.
  37. Bazire S. *Psychotropic Drug Directory 2002, The professionals' pocket handbook and aide memoire*, Mark Allen Publishing Ltd; 2001.
  38. Lam RW, Wan DD, Cohen NL, Kewnnedy SH. Combining antidepressants for treatment-resistant depression, *J Clin Psychiatry* 2002;63:685-93.
  39. Berk M, Ichim C, Brook S. Efficacy of mirtazapine add on therapy to haloperidol in the treatment of negative symptoms of schizophrenia: a double-blind randomised placebo controlled study. *Int Clin Psychoiparmacol* 2001;16:87-92.
  40. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo controlled study of antidepressant augmentation with mirtazapine. *Biol Psychiatry* 2002;51:183-8.
  41. Loonen AJK. Lack of drug interaction between mirtazapine and risperidone in psychiatric patients: a pilot study. *Eur Neuropsychopharmacol* 1999;10:51-7.
  42. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 2001;158:131-4.
  43. Thase ME. What role do atypical antipsychotic drugs have in treatment resistant depression? *J Clin Psychiatry* 2002;63:95-103.
  44. Hirshfeld RM, Montgomery SA, Aguglia E, Amore M, Delgado PL, Gastpar M. Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. *J Clin Psychiatry* 2002;63:826-37.
  45. Sonawalla SB, Fava M. Severe Depression. Is There a Best Approach? *CNS Drugs* 2001;15:765-76.

*Received 29 November 2002, accepted 13 December 2002*