Antidepressants are indicated in about 40 different disorders, including mood disorders, anxiety disorders, and other disorders. We propose to call these disorders antidepressant-responsive disorders (ARDs). We describe the clinical and biological criteria that differentiate the antidepressants. Although antidepressants share the same clinical efficacy in most ARDs, the configuration of adverse drug reactions varies widely. The recent antidepressants should be preferred to the tricyclic antidepressants as first-line treatment because of their lesser risk of severe adverse drug reactions. However, several recent antidepressants have been associated with severe complications such as the serotonin syndrome and the withdrawal syndrome. Patient characteristics should be included as a criterion to predict both unwanted and favorable effects.

Keywords: antidepressant; classification; mode of action; efficacy; side effect

From: the Clinical Psychopharmacology Unit, Department of Psychiatry, Geneva University Hospital, Switzerland
Address for correspondence: Prof Pierre Schulz, Head of Clinical Psychopharmacology Unit, Department of Psychiatry, Geneva University Hospitals (HUG), Chemin du Petit-Bel-Air 2, CH-1225, Chêne-Bourg, Geneva, Switzerland
E-mail: schulz-pierre@diogenes.hcuge.ch
said for the links between depression and the physiology of mood. ADs are useful in many disorders that are not classified as mood disorders; in fact, there are more than 40 different antidepressant-responsive disorders (ARDs). This can be explained in part by taking into account the fact that many higher brain functions are involved in the composite concept of mood, and that these functions can be altered in other psychiatric disorders as well. Anxiety disorders, one of the categories of ARDs, could be viewed as disorders of the normal function of anticipation of the future or of detection of danger. Obsessive-compulsive disorder appears to be a disorder where the safety of successive conditions and of the consequences of one’s behaviors cannot be recognized by the subject. These introductory remarks illustrate that ADs are medications that act on higher brain functions, ie, they exert a pharmacological action on the highly abstract functions that enable us to construct multimodal representations of the world and adapt our behavior.

Criteria for the classification of antidepressants

Many criteria can be used to classify and compare ADs. These are summarized in Table I. Some degree of overlap can exist between these criteria. ADs are medications for the treatment of mood disorders. This truism is more complex than appears at first glance. Indeed, there are more than 20 different types of depressive disorders, such as major depressive episode with melancholic features, seasonal features, or postpartum onset, premenstrual dysphoric disorder, brief recurrent depressive disorder, depression in bipolar mood disorder, depression due to an endocrine or other general medical condition. Anxiety disorders should be added to the list of ARDs, because these disorders respond to the more recent ADs. ADs are also indicated in bulimia nervosa, conduct disorders in mental deficiency or dementia, depression in schizophrenia, fibromyalgia, enuresis, and other disorders.

Clinical efficacy of antidepressants

Positive aspects of antidepressants in general

All molecules that meet the definition of ADs have the capacity to change in a radical and positive way the life of subjects suffering from mood disorders. Prevention of relapses and prevention of suicide attempts are also positive characteristics that are common to all ADs. When the aim is not to treat an acute depressive episode, but to suppress long-lasting suffering related to panic attacks, dysthymia, or phobias, the new ADs have the advantage, because they have been studied more extensively in these indications, and because of their lesser risk of severe adverse drug reactions. Comorbidity is frequent, for example, in cases where dysthymia or chronic depression is thought to originate in social isolation resulting from social phobia or an avoidant personality disorder.

Table I. Criteria for the comparison of antidepressants.

| Clinical efficacy | Adverse drug reactions | Pharmacological modes of action | Pharmacokinetics | Patient characteristics | Costs |
|-------------------|------------------------|---------------------------------|------------------|------------------------|-------|

In view of the multitude of ADs and of their indications, we propose to coin the word “disorderogram,” and distinguish two types thereof: those centered on a disorder and those centered on an AD. Disorder-centered disorderograms look at the comparative efficacy of ADs in the management (treatment of acute manifestations and prevention of relapses) of a given disorder, whereas AD-centered disorderograms look at the efficacy of a given AD with respect to the whole range of its indications (all ARDs). The total number of disorderograms is high, around 40 for the disorder-centered disorderograms and around 25 for the AD-centered ones (there are 25 ADs currently available on the Swiss market). Such a large amount of information makes it extremely difficult to make an exhaustive comparison between the different ADs. In the following, we will discuss the general aspects of the efficacy of ADs.

Figure 1. Depiction of despair according to Le Brun. Le Brun was a painter at the time of the French king Louis XIV. See text for his definition of despair.
Negative aspects of antidepressants in general

The efficacy of ADs in depressive mood disorders develops only after a delay of a few days to 4 weeks. Despite hopes and promises, no AD has been demonstrated to have a quicker onset of antidepressant efficacy. An average of 20% to 40% of patients with major depression do not respond to therapy, and there is no proof that any given drug is more efficacious than any other. The debate over clinical efficacy in the difficult-to-treat cases of severe depression or depression with melancholic or psychotic characteristics is still unresolved, with some publications indicating superiority of tricyclic antidepressants (TCAs), while other studies or meta-analyses report recent ADs to have equal efficacy. Comparison of studies is complicated by the fact that the rate of drug response varies between studies, from low values, in the order of 30%, to very high values of 70% or more. In some studies where TCAs were found to have greater efficacy than recent ADs, the dosage of the latter may have been too low. The issue of clinical superiority of a given AD in other ARDs is also complex, with the exception that ADs that influence the serotoninergic system are more efficacious in obsessive-compulsive disorder than those acting selectively on noradrenergic systems.

Adverse drug reactions

This criterion of comparison between ADs is the one most relevant to clinical practice, since the differences in efficacy between ADs are so minimal.

Positive aspects of recent antidepressants

Recent ADs show less frequent and less severe adverse drug reactions. With a classic TCA such as amitriptyline, administration of a daily dosage of 100 to 200 mg will induce sedation, dry mouth, constipation, hypotension, impairment of psychomotor performance (choice reaction time or critical flicker/fusion frequency) persisting even when the subjective feeling of sedation has worn off, intracardiac conduction disturbances, and risk of convulsions. These adverse reactions are the reason why the dosage of TCAs has to be achieved progressively, over several days. Because of these adverse reactions, the patient may have to stay off work for longer periods of time with TCAs than with recent ADs. These drugs may also induce weight gain of over 10 kg in several weeks and impaired sexual function, which are a source of distress to patients. Although the adverse reactions of recent ADs may occasionally be experienced by patients as disagreeable and troublesome, they are less frequent and less severe than those of the TCAs. This advantage is borne out by some patients treated with recent ADs who report no medication-related unwanted effects, a degree of patient satisfaction paralleled only rarely by the TCAs. Further confirmation comes from clinical trials indicating a patient dropout rate of ≥15% with recent ADs compared to ≥20% with TCAs, and clinical practice data based on 13619 prescriptions, which showed dropout rates of 22% and 33%, respectively. Mortality after suicide attempts is almost nonexistent with the newer ADs, while it was between 0.5% and 4% of patients who were hospitalized after a failed suicide attempt in cases of TCA overdose.

Negative aspects of recent antidepressants

The adverse drug reactions observed with recent ADs include tremor, nausea, diarrhea, vertigo, sweating, headache, impaired sexual function, sleep fragmentation, anxiety, nervousness, akathisia (inability to remain in sitting posture, restlessness, muscular quivering, anxiety, irritability), iatrogenic mania, withdrawal symptoms, and the serotonin syndrome. These adverse drug reactions do not occur with all the recent ADs. For example, sedation is typical of nefazodone and mirtazapine, and these ADs also induce dry mouth. Nefazodone does not induce sleep fragmentation, in contrast to the selective serotonin reuptake inhibitors (SSRIs). Mirtazapine causes weight gain, in contrast to most of the newer ADs like the SSRIs and venlafaxine, which induce a loss of appetite and an increase in whole body metabolism, usually resulting in little weight change, although some patients may lose or gain weight because of the treatment. Among the recent ADs, fluoxetine, sertraline, moclobemide, and bupropion are the less sedating molecules, the first two even increase choice reaction time in normal volunteers. Sexual adverse reactions, when they occur, are generally a minor problem for the patient during the acute phase of the treatment of a depressive disorder, but they are bothersome during the maintenance phase. The SSRIs (with the possible exception of fluvoxamine) are associated with a higher incidence of sexual dysfunction than nefazodone, moclobemide, or mirtazapine. Bupropion, which influences the dopaminergic system, can activate the libido. Recent ADs can induce hypomania or mania in some subjects, a phenomenon referred to as the “iatrogenic switch.” This may also occur with TCAs and some nonpharmacological therapies such as sleep deprivation or electroconvulsive...
The serotonin syndrome is a severe adverse drug reaction associated with the occurrence of massive and frequent symptoms, making it difficult to distinguish from sertraline or placebo. The rare instances of addiction to ADs have been associated with the possible exception of the nonselective irreversible monoamine oxidase inhibitors (MAOIs) or the dopaminergic antidepressants, which have a very low risk of recurrence. Treatment with ADs, with the possible exception of the nonselective irreversible monoamine oxidase inhibitors (MAOIs) or the dopaminergic antidepressants, for which a very low risk may exist in some predisposed subjects. ADs, therefore, do not appear to be addictive. The mode of action of a psychotropic medication can be analyzed at several levels, from the macroscopic to the biochemical.

**Mode of action**

The mode of action of a psychotropic medication can be analyzed at several levels, from the macroscopic to the biochemical.

**Psychological mode of action**

An important problem is to determine the specificities of the psychological mode of action of ADs, in other words, to determine which ones are more effective, eg, in improving the capacity to experience pleasurable events or in reducing the tendency to perceive only the potential dangers or nega-
Pharmacological aspects
tive aspects of life, and which ones appear to enhance the ability to engage in rewarding social relationships, or improve cognitive impairment or vigilance and attention. In our opinion, most or all of the above effects contribute to the antidepressant effects of ADs, but there are very few studies investigating how ADs modify the different higher brain functions mentioned above, although such studies would be very useful, if only because of the implications in terms of how ADs are marketed. Reboxetine is a case in point. Reboxetine was found to have no greater anxiolytic or antidepressant efficacy than fluoxetine in several comparative trials, but when a scale for the self-evaluation of social adaptation was applied, this selective inhibitor of the norepinephrine presynaptic transporter was found to be superior to fluoxetine. However, this difference will have to be confirmed before too many hypotheses are made about the respective roles of serotonin and norepinephrine in social functioning!
Another aspect is how ADs are characterized in terms of adverse drug reactions. Some ADs are sedative, others are stimulating; most can induce anxiety during the first days of treatment (and this is a reason to use low doses of SSRIs during the first days of treatment of anxiety disorders).

Neurophysiological mode of action
ADs influence the serotonergic, noradrenergic, and dopaminergic systems. These systems act through mass transfer of information: this means that they act little via point-to-point synapses, but rather influence segments of other brain areas in a global manner through the release of neurotransmitters in the interstitial fluid. Examples of major groups of cells or nuclei that contain these neurotransmitters are the locus ceruleus for norepinephrine, the raphe nuclei for serotonin and norepinephrine in social functioning! Another aspect is how ADs are characterized in terms of adverse drug reactions. Some ADs are sedative, others are stimulating; most can induce anxiety during the first days of treatment (and this is a reason to use low doses of SSRIs during the first days of treatment of anxiety disorders).

Biochemical mode of action
The biochemistry of neurotransmitter release and uptake in the synapse includes the following major steps. A series of precursor molecules are synthesized, the neurotransmitter is stored in intracellular vesicles, which then release it into the synaptic cleft. A presynaptic membrane protein serves as transporter for the neurotransmitter, ensuring its reuptake, and this reuptake is the main level where the influence of the neurotransmitter on the postsynaptic receptors can be inhibited. Some presynaptic receptors exert an inhibitory effect on neurotransmitter release when activated by the neurotransmitter. Finally, at the postsynaptic level, a cascade of events follows the binding of neurotransmitters or other ligands to the membrane receptors. This leads to changes in cytoplasmic chemical signaling systems and subsequent synthesis of new peptides. ADs, like other psychotropic medications or addictive drugs, can act at any of these biochemical steps, and each AD has a distinctive “enzymogram,” “receptorogram,” and “transporterogram.” These configurations of biochemical or pharmacological modes of action are well described in the literature. A TCA such as amitriptyline inhibits the serotonin and norepinephrine transporters, and this probably explains its antidepressant effects. Amitriptyline also antagonizes the cholinergic muscarinic receptors (all types), the histaminergic H1 and H2 receptors, the 5-HT2 receptor, and the α1-adrenergic receptor. It slows down intracardiac electrical conduction and inhibits prostaglandin synthesis. These multiple actions explain why amitriptyline can improve duodenal ulcer, lower arterial hypertension, prevent recurrent migraine, and improve ventricular extrasystoles, pruriginous skin disorders, nocturnal enuresis, and premature ejaculation. These clinical effects can all be explained on the basis of the “enzymogram,” “receptorogram,” and “transporterogram” of amitriptyline, rather than by psychosomatic theories. Amitriptyline has been shown to be effective even after cutaneous application in cases of pruriginous dermatitis, thus providing a strong argument against the idea that ADs improve the symptoms of these disorders through a central action on so-called masked depression. Compared to
TCAs, SSRIs and other recent ADs have more restricted “enzymograms,” “receptorograms,” and “transporterograms,” despite their having more than a single mode of action. While all SSRIs antagonize the serotonin transporter, fluoxetine also inhibits the 2D6 cytochrome P450 enzymes and possibly also peripheral and central cholinergic and nictinic receptors, as well as 5-HT_{2C} receptors. Sertraline may act on dopamine and on sigma systems. ADs also influence neuroendocrine systems. For example, some TCAs inhibit the synthesis of corticotrophin-releasing hormone (CRH) mRNA, as well as activating the synthesis of glucocorticoid receptor mRNA in the hippocampus. These actions amount to a lowering of the activity level in a major endocrine axis involved in stress responses. TCAs and other ADs might thus act as “antistress” molecules. Amitriptyline also increases luteinizing hormone–releasing hormone (LH-RH) mRNA. Taken together, these findings are of interest since increased cortisol and decreased testosterone secretion have been associated with severe depression. Few ADs have been studied in this connection. Some findings are inconsistent, in the sense that some clinically effective ADs do not downregulate the axis leading to the secretion of cortisol. Other compounds, such as interferon and the interleukins (IL-1, IL-6) are also interesting to study in relation to ADs, because these substances can stimulate the hypothalamo-hypophyseal-adrenocortical axis. Other sites of potential pharmacological actions of ADs are the recently discovered anandamide, an endogenous ligand to the cannabis receptor. ADs may also act on sigma receptors, glutamatergic systems (glycine site on the N-methyl-D-aspartate [NMDA] receptor), cholinergic systems, substance P, and neurotrophins. The data on AD “enzymograms,” “receptorograms,” and “transporterograms” are extensive; they provide useful help in understanding many of the clinical effects of ADs, but they are permanently being updated, which makes the comparison between ADs on the basis of their biochemical mode of action a difficult challenge. The multiple biochemical effects of ADs are still impossible to integrate into a single explanation of their mode of action. Current hypotheses suggest the existence of a common final pathway for the monoamine and neuroendocrine systems or a mechanism involving remodeling of defective synapses.

**Pharmacokinetics**

There are few differences in pharmacokinetics between ADs. One major difference is the elimination half-life (T1/2). For example, venlafaxine has a very short half-life of only a couple of hours, while fluoxetine has a very long one of several days. The clearance of ADs is decreased in patients over 70 years of age and in severe hepatic insufficiency. Renal insufficiency leads to high concentrations of the hydroxylated and conjugated metabolites, but this has few proven clinical consequences. Several ADs inhibit different cytochrome P450 enzymes, and this can lead to adverse drug reactions when patients are receiving multiple drugs. Among the recent ADs, citalopram, moclobemide, and sertraline induce little enzymatic inhibition of this type.

**Influence of patient characteristics**

Patient characteristics can modify the effects of ADs. These differences are such that the same SSRI may be judged by one patient as absolutely free of any adverse drug reaction, while another patient will complain of a long list of adverse reactions and will have to discontinue the medication. In some cases, drug monitoring has shown that individual differences in intensity of response to ADs are not obligatorily of pharmacokinetic origin, in the sense that subjects with AD concentrations in the lower ranges can show adverse drug reactions, while subjects with concentrations in the higher ranges have no complaints. There is little information on the dose-response curves of psychotropic medications in individual patients. This means that, while we know that the clearance of ADs can vary between patients by a factor or up to 5 or more, we do not know the quantitative range of variation of sensitivity to the beneficial or deleterious effects of ADs. It might be that some populations of patients have very little chance of benefiting from treatment. A situation of this type was identified in relation to the prevention of myocardial infarction (relapse rate) 3 years after a first infarction. Overall, propranolol had a protective effect of 3% (reinfarction rate of 12% with propranolol and 9% with placebo). But the relapse rate was 6% in subjects with a high educational level compared to 13% when this level was low, and 2% in subjects with low stress and social isolation compared to 14% when these were high. These findings in the field of cardiology suggest that financial, social, or educational measures might be more effective than drug treatment in disadvantaged patients groups. How this concept applies to AD treatment is still unclear.

It is possible that the risk of developing psychiatric adverse drug reactions is dependent on the patients more than the drugs themselves. For example, hyperthyemic personality might be an independent risk factor for drug-induced hypomania. The rule of baseline characteristics states that if a patient presents with a preexisting physical abnormality before treatment, then the
risk of an iatrogenic reaction having the characteristics of this abnormality is greatly increased. Thus, an elderly patient with age-related cognitive decline will be more sensitive to the amnestic effects of anticholinergics or benzodiazepines, and a patient with orthostatic hypotension will be more sensitive to the hypotensive effects of medications. With ADs, the rule of baseline characteristics is probably predictive of a greater risk for most adverse drug reactions. Interindividual differences are the domain of pharmacogenetic studies, and the hope is that better knowledge of genetic polymorphism will facilitate the prediction of both the favorable and adverse effects of drugs.

Cost of antidepressant therapy

Health care costs have long been a cause for concern and, indeed, there is no room for euphoria when health care costs are soaring to more than 10% of gross national products in some Western countries. In 1978, the Palo Alto Times published a cartoon in which Cicero was playing the part of a doctor being asked by Bugs Bunny: “How sick am I doc?” Cicero’s answer was: “That depends on how well you are insured.” Health economists have conflicting interests; each individual, each institution wishes to maximize its benefits and minimize its losses, with little consideration for the health and well-being of the nation as a whole. In Switzerland, a well-known insurance company gave a regrettable confirmation of this sad state of affairs when they stopped providing the basic mandatory insurance package in Swiss cantons where health expenditure was judged to be too high. The American public holds the belief that “managed care has killed patient care.” Yet nobody would like to see renal transplants or access to intensive care units being denied to citizens above 65 years of age, as tended to be the case 25 years ago in Geneva.

Coming back to the costs of AD therapy, as only a small proportion of patients with ARDs are currently being treated, their number stands to increase, and costs, therefore, likewise. If we look at the pharmacoeconomics of ADs, it is obvious that the older ADs are less costly, ie, a dosage of 2 tablets a day of a recent AD can cost more than twice the price of 150 mg per day of a TCA (incidentally, the average $200 cost for 100 tablets of the recent AD is equivalent to the monthly salary of a psychiatrist in many countries from the former Soviet Union bloc). This high price of the newer ADs raises the issue of the comparison of the costs of pharmacotherapy and psychotherapy. In Switzerland, the cost of a twice-daily dosage of tablets of the newer ADs is a quarter to a third of a weekly psychotherapy session with a psychiatrist, and half the cost of a weekly session with a psychologist. Despite the fact that the newer ADs are more expensive, pharmacoeconomic analysis shows them to be advantageous. This conclusion is based on the fact that these drugs are associated with a smaller number of accidents, that adverse reactions caused by them necessitate fewer medical interventions (as opposed, for example, to TCAs, which can lead to urinary obstruction requiring urinary catheterization, with the risk of secondary infection). The global cost of ARD therapy is therefore in the recent ADs’ favor, but the margin of this advantage is small, in the range of 5% and rarely more than 20%, depending on the models chosen for the calculation.

Conclusion

No AD seems to be significantly superior to any other in terms of clinical efficacy. All have a delayed onset of beneficial effects, and all influence indolamines or catecholamines in one way or another. However, the differences between ADs outnumber their similarities, and this has implications for the choice of treatment. We recommend prescribing the recent ADs as first-line treatment, and that TCAs should be given only in the event of treatment resistance. We recommend basing therapeutic choices on the “disorderogram,” the configuration of adverse drug reactions, and the configuration of pharmacological actions (“receptorogram,” “enzymogram,” “transporterogram”). These pharmacological data are constantly being updated by new findings, but they provide a useful basis for the choice of compounds that will provide clinical efficacy against ARDs.
¿Son iguales todos los antidepresivos?

Existen alrededor de 40 trastornos en los que se prescriben antidepresivos, entre los cuales se incluyen los trastornos afectivos, trastornos ansiosos, y otros. Proponemos llamarlos «trastornos que responden a antidepresivos» (antidepressant-responsive disorders, ARDs). Se describen los criterios clínicos y biológicos que diferencian los antidepresivos. A pesar de que en la mayoría de los ARDs los antidepresivos comparten la misma eficacia clínica, la configuración y las reacciones adversas de cada fármaco varían ampliamente. Se debería preferir los antidepresivos recientes a los antidepresivos tricíclicos en la prescripción de un tratamiento de primera elección, dado que presentan un riesgo menor de reacciones adversas. Sin embargo, varios antidepresivos recientes han sido relacionados con complicaciones severas tales como el síndrome serotoninérgico y el síndrome de abstinencia. Deben incluirse las características del paciente como criterio de predicción tanto de los efectos deseados como beneficiosos.

Les antidépresseurs sont-ils tous pareils?

Les antidépresseurs sont indiqués dans environ une quarantaine de troubles différents, tels les troubles de l’humeur, les troubles anxieux, etc. Pour désigner l’ensemble de ces troubles, nous proposons l’appellation «antidepressant-responsive disorders», soit «troubles répondant à l’action des antidépresseurs». Dans cet article sont énoncés les critères cliniques et biologiques permettant de différencier les antidépresseurs. Alors que l’efficacité de ces médicaments dans les différents troubles évoqués ci-dessus est grossièrement identique, tel n’est pas le cas de leurs profils d’effets indésirables où des différences notables existent. La famille des tricycliques doit désormais céder la place aux antidépresseurs récents pour ce qui concerne le traitement de première intention eu égard à la plus faible incidence des effets indésirables rencontrés avec ces derniers. Cependant, il faut noter que certains antidépresseurs récents ont pu être associés à des complications graves du type syndrome sérotoninergique ou syndrome de sevrage. Les caractéristiques des patients jouent également un rôle essentiel pour prédire les effets aussi bien bénéfiques qu’indésirables liés à l’utilisation des antidépresseurs.

REFERENCES

1. Kuhn R. Über die Behandlung depressiver Zustände mit einem Imino-dibenzylderivat (G 22355). Schweiz Med Wochenschr. 1957;87:1135-1140.
2. Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. Depress Anxiety. 1998; 7(suppl 1):11-17.
3. Angst J, Amrein R, Stabl M. Moclobemide and tricyclic antidepressants in severe depression. Meta-analysis and prospective studies. J Clin Psychopharmacol. 1995;15(suppl 2):16-23.
4. Martin RM, Hilton SR, Kerry SM, Richard NM. General practitioners’ perceptions of the tolerability of antidepressant drugs: a comparison of selective serotonin reuptake inhibitors and tricyclic antidepressants. Br Med J. 1997;314:646-651.
5. Armitage R, Yonkers K, Cole D, Rush AJ. A multi-centre, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. J Clin Psychopharmacol. 1997;17:161-168.
6. Zavertailo LA, Busto U, Kaplan HL, Sellers EM. Comparative abuse liability of sertraline, alprazolam, and dextroamphetamine in humans. J Clin Psychopharmacol. 1995;15:117-124.
7. Lane R, Fischler B. The serotonin syndrome: coadministration, discontinuation and washout periods for the selective serotonin reuptake inhibitors (SSRIs). J Serotonin Res. 1995;3:171-180.
8. Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake withdrawal. J Clin Psychopharmacol. 1996;16:356-362.
9. Tyrer P. Clinical effects of abrupt withdrawal from tricyclic antidepressants and monoamine oxidase inhibitors after long-term treatment. J Affect Disord. 1984;6:1-7.
10. Dilsaver SC. Antidepressant withdrawal syndromes: phenomenology and pathophysiology. Acta Psychiatr Scand. 1989;79:113-117.
11. Dubini A, Bosc M, Polin V. Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. J Psychopharmacol. 1997;11(suppl 4):17-23.
12. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. N Engl J Med. 1984;311:552-559.
13. Stewart A. Cost-effectiveness of SSRIs: a European perspective. J Ment Health Policy Econ. 1998;1:41-49.