Anxiety and depression

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Summary

Objectives

The DSM-5 classifies depressive and anxiety disorders according to clinical symptoms and assesses possible correlations with a medical condition, use of psychoactive or pharmacological drugs, or substance abuse. The objective of the present review is to overview the main depressive and anxiety disorders according to the classification of the DSM-5 and to present the primary pharmacological and non-pharmacological treatments, with particular emphasis on the problem of compliance.

Methods

Literature review of recent years on depressive disorders and anxiety disorders was carried out following publication of the DSM-5 (2013).

Results

In the DSM-5, depressive disorders include disruptive mood dysregulation, major depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder, depressive disorder induced by substances/drugs, and depressive disorder due to other medical conditions. The common characteristic of these conditions is the presence of sad, empty, or irritable mood, which together with specific cognitive and somatic symptoms leads to significant distress or impairment in functioning. The anxiety disorders recognised in the DSM-5 include separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalised anxiety disorder, anxiety disorder induced by substances/drugs and anxiety disorder due to another medical condition. All the disorders share characteristics of excessive fear and anxiety correlated with behavioural alterations. In anxiety disorders, the stimulus, external or internal, produces a disproportionate anxious reaction that is a source of intense distress or significant impairment of functioning. Pharmacological therapy alone, psychotherapy alone, or the combination of both are efficacious in the treatment of depression, generalised anxiety disorder, panic attacks and insomnia. It is important to involve the patient in the therapeutic course through adequate communication and information about time to therapeutic response and possible side effects. SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin-norepinephrine reuptake inhibitors) are first-choice agents in the treatment of depression, with demonstrated efficacy and safety. A benzodiazepine can be used in the first 4 weeks of therapy for depression in the presence of significant symptoms of anxiety, in panic disorder and insomnia to obtain rapid improvement in symptoms. In the treatment of depressive disorders, compliance is important to achieve the objectives of antidepressant therapy. In recent years, significant progress has been made in identification of risk factors for poor compliance and development of a variety of strategies aimed at increasing adherence to therapy, especially in improving communication, patient education, dose optimisation and scheduled follow-up.

Conclusions

In treatment of depressive and anxiety disorders, therapeutic choice should consider patient preferences and must be decided together with the patient. Compliance is an important aspect that determines the success of treatment.

Key words

Depression • Anxiety • Compliance • DSM-5

The DSM-5 and clinical utility

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Introduction: the DSM-5 in clinical practice

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is likely the most well-known and used diagnostic reference in psychiatry. Its descriptive and nontheoretical nature make it easy to use, and no specific theoretical training is needed to use it. In the DSM-5, psychiatric disorders are grouped into broad categories (such as psychotic disorders, depressive disorders, anxiety disorders, etc.) within which the individual disorders are described. Each disorder is diagnosed on the basis of grouping of symptoms. To allow a diagnosis of mental disorder, a particular group of symptoms must be present, which are related to impairment of functioning and/or to significant discomfort. For many disorders, such as depressive disorders and anxiety disorders, 'essential' clinical features are distinguished from those caused by a concomitant medical condition or use of drugs or psychoactive substances.

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The diagnostic course in clinical practice

When applied to depressive disorders and anxiety disorders, two phases are primarily used for diagnosis in the DSM-5:

1. classify the disorder based on objective psychological examination and patient-reported signs and symptoms;
2. evaluate if the symptoms may be correlated with a medical condition, use of psychoactive or pharmacological drugs, or substance abuse.

The first phase involves listening to subjective experiences of the patient together with psychological examination. By grouping symptoms, the disorder can be defined. The second phase involves assessing for potential somatic or exogenous causes of the psychic disorder. A variety of physical diseases can give rise to depression and anxiety. In some cases, depressive and anxious symptoms are characteristic of an underlying medical disease and present as the first manifestations of somatic disease. For example, loss of appetite, weight loss, fatigue and depressed mood in older patients can be symptomatic of pancreatic cancer. In other cases, anxiety and restlessness associated with vegetative symptoms may be caused by onset of hyperthyroidism. In some cases, depression or anxiety may be related to a previously diagnosed disease, as in certain neurological and endocrine disorders. Lastly, depression and anxiety may be caused by pharmacological treatment, a psychoactive drug, or by their discontinuation. Interactions between susceptibility and stressful events may generate diverse symptoms that are accurately classified in the DSM-5. The main clinical pictures of depressive and anxiety disorders according to the DSM-5 are detailed below.

Depressive disorders in the DSM-5

Depressive disorders in the DSM-5 include disruptive mood dysregulation, major depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder, depressive disorder induced by substances/drugs and depressive disorder due to other medical conditions. The common characteristic of these conditions is the presence of sad, empty, or irritable mood, which together with specific cognitive and somatic symptoms, leads to significant distress or impairment in functioning. Disruptive mood dysregulation disorder is diagnosed in children who show severe and frequent outbursts of anger, which are grossly disproportionate to the triggering event, and associated with persistent irritated or sad mood that occurs in different contexts, for example at home and at school. Diagnosis requires that the onset is before the age of 10 years. It is believed that this set of symptoms can constitute the expression of major depressive disorders in early childhood, also considering the strong association with later development of these disorders in adulthood. Major depressive disorder is characterised by the presence of episodes of persistently depressed mood and/or a diminished ability to experience pleasure, associated with at least five of the following symptoms: significant changes in appetite or weight, insomnia or hypersomnia, psychomotor agitation or retardation, weakness and easy fatigue, feelings of worthlessness or guilt, decreased concentration and memory impairment, thoughts of death. Symptoms must be present daily for at least 2 weeks, and depressed mood must be present for most of the time. Major depressive disorder is often recurrent and characterised by episodes throughout life. Onset is usually between the ages of 20 and 30 years and is up to 3 times more frequent in women. It Italy, about 8-10% of the general population is affected.

Persistent depressive disorder is defined by its chronic course, characterised by the presence of persistently low mood for at least 2 years and associated with two or more of the following symptoms: poor or increased appetite, insomnia or hypersomnia, low energy and fatigue, low self-esteem, difficulty in concentrating and feelings and beliefs of hopelessness. Persistent depressive disorder has a prevalence of 2-3%, is more frequent in late adolescence or early adulthood and often associated with personality disorders and substance abuse. Premenstrual dysphoric disorder has phasic fluctuations and appears in the week prior to the menstrual cycle. It tends to resolve during the first days of menstruation. The disorder is characterised by marked affective lability, associated with deflected and irritable mood, increased sensitivity to rejection and tendency to interpersonal conflicts. It is associated with changes in appetite and sleep, lethargy and fatigue, and physical symptoms such as bloating or tension, muscle and joint pain. Its prevalence is about 1.3-1.8%.

Depressive disorder due to substances/drugs is characterised by the presence of low mood and loss of interests that appear during or shortly after intoxication or discontinuation of the responsible agent, or during exposure to a drug. It cannot be diagnosed in cases of depressive symptoms lasting more than 1 month after the discontinuation of the substance/drug. Various abused substances, such as alcohol, opioids, sedative drugs, cocaine or other stimulants, and hallucinogens, can induce depressive symptoms. Regarding the association between drugs and depression, depressive symptoms are associated with treatment with interferon-α, corticosteroids, interleukin-2, GnRH, mefloquine, contraceptive implants that release progesterone and cardiovascular drugs such as methyldopa, clonidine, propranolol and sotalol. A recent study on the reporting of drug-related adverse events

in the UK from 1998-2011 found an association between depression and use of isotretinoin, rimonabant and varenicline. In Italy, there are no data on the prevalence of depressive disorders induced by substances/drugs, while in the US it has been estimated that the prevalence is 0.26%.

Lastly, depressive disorder due to other medical conditions can be diagnosed when depressive symptoms are the direct pathophysiological consequence of another medical condition. In some cases, the association between an underlying disease and depression is very strong, and common pathophysiological links have been demonstrated in the two conditions. This is the case with neurological conditions such as stroke, Parkinson's and Huntington's diseases, cranial trauma and multiple sclerosis as well as with endocrinopathies such as Cushing's disease and hypothyroidism. In other cases, if the onset of depression is a response to stress related to an underlying disease, it is more correct to diagnose adjustment disorder with depressed mood.

Anxiety disorders in the DSM-5

Anxiety disorders share the characteristics of excessive fear and anxiety and related behavioural alterations. In anxiety disorder, the stimulus, external or internal, produces a disproportionate anxiety that is the source of intense distress or significant impairment of functioning. Another characteristic of anxiety disorders is anxious anticipation, or rising levels of concern and tension at the approach of a feared situation, and avoidance of stimuli or situations that trigger anxiety, with further limitations in functioning. The anxiety disorders recognised in the DSM-5 include separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalised anxiety disorder, anxiety disorder induced by substances/drugs and anxiety disorder due to another medical condition. Separation anxiety disorder is diagnosed in children who have disproportionate anxious reactions to separation, even temporary, to attachment figures, especially parents. The disorder can even last into an adult age. Children with separation anxiety manifest the fear of losing their parents, refusal or reluctance to be alone, unwillingness to go outside for fear that an external event might separate them from their parents, or to sleep away from home. Affected children may also report nightmares and somatic complaints. Separation anxiety disorder is diagnosed if three or more of the following symptoms are present for at least 4 weeks, or for 6 months in adults. In Italy, 2% of children suffer from separation anxiety disorder, with frequent onset at preschool age.

Selective mutism is diagnosed in children who do not speak in certain social situations, for example at school, which is related to high levels of social anxiety or excessive shyness, and not to linguistic or intellectual deficits. Selective mutism is a rare disorder, with a prevalence of 0.03-1%.

Specific phobias are characterised by excessive or unreasonable fear of an object or situation, disproportionate to the actual danger, to which exposure leads to intense anxiety. The object or situation feared is actively avoided. Diagnosis of a specific phobia can be considered when the duration is at least 6 months. The most frequent phobias are those of animals (spiders, insects, dogs, etc.), natural (heights, storms, etc.), needles/blood and situations (aeroplanes, elevators, etc.). In Italy, about 6% of the population suffers from a specific phobia over their lifetime, with onset normally around the age of 10 years. Social anxiety disorder is characterised by fear of finding oneself in certain social situations. Some examples are speaking in a group of people, eating or drinking in public, or carrying out specific tasks. An individual with social anxiety is afraid of failing in certain situations and then be judged, ridiculed, or criticised by others. For this reason, the person frequently avoids contact in the feared social situation. Even in this case, symptoms must be present for at least 6 months. In Italy, about 2% of the population suffers from

TABLE I.
Depressive and anxiety disorders in the DSM-5.

Depressive disorders	Anxiety disorders
Disruptive mood dysregulation disorder	Separation anxiety disorder
Major depressive disorder	Selective mutism
Persistent depressive disorder	Specific phobia
Premenstrual dysphoric disorder	Social anxiety disorder
Depressive disorder induced by substances/drugs	Panic disorder
Depressive disorder due to another medical condition	Agoraphobia
	Generalised anxiety disorder
	Anxiety disorder induced by substances/drugs
	Anxiety disorder due to another medical condition

TABLE II.
Drugs that can induce depressive and anxiety disorders.

Depressive disorders	Anxiety disorders
Interferon α-β Corticosteroids Interleukin-2 GnRH Contraceptive implants that release progesterone Cardiovascular (methyldopa, clonidine, propranolol, sotalol) Mefloquine Isotretinoin Rimonabant Varenicline	Corticosteroids Salbutamol Sympathomimetics Insulin Thyroid hormones L-Dopa

TABLE III.
Medical conditions that can cause depression and anxiety disorders.

Depressive disorders	Anxiety disorders
Stroke Parkinson's disease Huntington's disease Head injuries Multiple sclerosis Cushing's disease Hypothyroidism	Hyperthyroidism Hypoglycaemia Pheochromocytoma Cushing's disease Vitamin B12 deficiency Porphyria Cardiovascular disease (heart failure, atrial fibrillation) Pulmonary diseases (pulmonary embolism, asthma)

social anxiety disorder over the course of a lifetime, with onset generally at the start of adolescence at around 13 years.

Panic disorder is diagnosed in cases of recurrent or unexpected manic. Panic attack is a sudden episode of intense anxiety and discomfort, which reaches a peak in a few minutes and is associated with somatic symptoms such as palpitations, sweating, trembling, shortness of breath, choking sensation, chest pain, nausea, dizziness, numbness, fear of going crazy, or dying. In panic disorder, attacks are usually followed by the constant worry that they can recur or by concern about the consequences of attacks. Patients often actively avoid situations that can trigger the attacks, for example driving or visiting crowded places. Panic disorder is frequently associated with agoraphobia, or the fear of being in situations where it is difficult or embarrassing to escape in case of a panic attack: classically feared situations are being in crowded places (public transport, cinemas, supermarkets), open spaces, being in a queue of cars or people, or being outside the home alone. Finding oneself in the feared situation frequently triggers a panic attack, which is the reason for which such situations are avoided in individuals with agoraphobia. Panic disorder usually appears in a young adult age and is more frequent in young women, with a frequency that is about twice that in men. In Italy, the lifetime prevalence of panic disorder is 1.6%, and 1.2% for agoraphobia.

Generalised anxiety disorder is diagnosed in cases of excessive anxiety and worry related to a large number of daily activities. The worry of having to carry out such activities, controlled with difficulty, is associated with at least three of the following symptoms: constant restlessness, easy fatigue, difficulty in concentrating, muscle tension, interrupted or unsatisfactory sleep. On average, the disorder begins around the age of 30 years, although it frequently has onset in adolescence or older age. In Italy, the lifetime prevalence of generalised anxiety disorder is 1.9%.

Anxiety disorder due to substances/drugs is defined by the presence of anxiety or panic attacks that occur during or shortly after intoxication or withdrawal from a substance, or during exposure to a drug. It cannot be diagnosed if the anxiety symptoms persist more than one month after discontinuation of the substance/drug. Several substances cause symptoms of anxiety: caffeine, cannabis, cocaine, amphetamines and other stimulants. Even exposure to drugs, such as salbutamol, sympathomimetics, insulin, thyroid hormones, L-Dopa and corticosteroids, can trigger anxiety symptoms. In addition, abstinence from alcohol, opioids, anxiolytics and especially benzodiazepines is frequently related to anxiety symptoms.

Depressive disorder due to other medical conditions can be diagnosed when depressive symptoms are the direct pathophysiological consequence of another medical condition. Pathologies of the endocrine system and metabolic conditions can cause anxiety and panic attacks, for example hyperthyroidism, hypoglycaemia, pheochromocytoma, Cushing's disease, vitamin B12 deficiency and porphyria. Even cardiopulmonary conditions, such as heart failure, pulmonary oedema, asthma and some arrhythmias can cause anxiety disorder.

Conclusions

The use of a diagnostic manual to define mental disorders in defined categories has many advantages, such as simple classification of patient experiences in well-defined clinical pictures and ease of communication with col leagues. Finally, the availability of validated treatments for individual disorders allows, not only for the specialist but for the general practitioner, to establish an effective treatment, which in some cases can fully resolve referred symptoms.

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Pharmacological and non-pharmacological treatment

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Data from the international literature have shown that the majority of patients with major depression are treated by a general practitioner (GP) [1]. GPs more frequently prescribe SSRIs and SNRIs than tricyclic antidepressants and monoamine oxidase inhibitors (MAO-I) [2]; moreover, it has been demonstrated that the use of antidepressants is effective in improving symptoms in primary care settings [3]. The OsMed report from 2013 documented that SSRIs represent a first choice in terms of costs among drugs that act on the CNS in reimbursed treatment regimens, and are the most widely prescribed; however, data from HealthSearch 2011 reported that only 35.4% of patients in whom a problem with depression has been identified are prescribed an antidepressant.

The use of drugs that act through multiple pathways seems to be even more valid in borderline pathologies and in pathologies within the spectrum of comorbidity. Thus, given the documented efficacy of many drugs classified as 'antidepressants' on anxiety symptoms, when dealing with an anxious-depressive condition, these drugs may be useful for 'anti-depressive' pharmacological treatment. Clinical experience has shown that many depressed patients do not respond or show only partial response to antidepressants, with complete remission of symptoms seen in 30% to 65% of cases. In other words, considering the entire population treated for major depression, it is possible to affirm that:

- 20-30% achieve remission;
- 20-30% show a reduction of 50% in depressive symptoms without achieving complete remission (HAM-D > 7);
- 10-15% have a partial response, with 25-50% reduction in symptoms;
- 20-30% are non-responsive to therapy, with < 25% reduction in symptoms;
- in addition, 10-30% of the entire population does not respond to multiple pharmacotherapies and psychotherapies, and these subjects are at high risk of morbidity and mortality.

Scientific evidence suggests that depression is much more disabling and resistant to treatment the longer it continues over time, and that a chronic course and/or highly recurrent disorder is associated with an increased risk of substance abuse, physical illness, suicide risk and social difficulties [4]. Despite these considerations, to date clear and definitive criteria have not been identified for choice of optimal initial therapy or to substitute or modify ineffective or partially effective therapy. Research is hindered by the wide variability of clinical presentations of depression, which is in part also responsible for incorrect or delayed recognition of the disease.

The main goals of treatment are:

- eliminate depressive symptoms;
- reduce or eliminate associated impairment;
- improve the quality of life and psychosocial functioning;
- prevent relapses and recurrences.

The objectives of initial treatment of major depression is remission of symptoms and improvement of the quality of life and psychosocial functioning. For initial treatment of a patient with mild-moderate depression there are several therapeutic strategies that involve the use of antidepressants alone, psychotherapy alone or combined antidepressant/psychotherapy. Randomised trials have shown that combined antidepressant/psychotherapy is more effective than either of the individual approaches alone [5]. Notwithstanding, additional studies have indicated that pharmacological therapy or psychotherapy alone are also valid choices; moreover, the efficacy of the two therapies is comparable. It is important to decide on the therapeutic course together with the patient, whose preferences can influence choice of therapy. In addition, complete evaluation of the patient must also include all aspects that could interfere with the therapeutic objective (previous therapies, comorbidities and psychosocial stressors). For patients with mild-moderate depression, treatment with SSRIs is recommended as first-line; these recommendations are based on the

TABLE I.
Antidepressant drugs, initial dose and therapeutic dose.

Drug	Initial dose (mg)	Therapeutic dose (mg)
SSRI		
Citalopram	20	20-40
Escitalopram	10	10-20
Fluoxetine	20	20-60
Fluvoxamine	50	50-200
Paroxetine	20	20-40
Sertraline	50	50-200
SNRI		
Duloxetine	30-60	30-120
Venlafaxine	37,5-75	75-375
Atypical antidepressants		
Buproprion	150	300
Mirtazapine	15	15-45
Serotonin modulators		
Trazodone	100	200-500

demonstrated efficacy and better tolerability of SSRIs [6]. SNRIs (e.g. venlafaxine, duloxetine), atypical antidepressants (e.g. bupropion, mirtazapine) and serotonin modulators (e.g. trazodone) can be used as alternatives to an SSRI.

Tricyclics and MAO-Is are not recommended as first-line treatment due to their poorer safety profile and increased incidence of adverse events. A meta-analysis in 2011 showed that there is no evidence in the choice of a second-generation SSRI in terms of improvement of symptoms (Tables I, II) [7].

Pharmacological treatment of depression should consider critical aspects. First, the severity of depression, for which antidepressants show significant benefits over placebo, has not been clearly defined. In general, the more severe the symptoms the greater the benefits of treatment. Antidepressants are nonetheless normally recommended as first-choice treatment in patients in whom depression is at least of moderate intensity. Secondly, there is large variability in tolerability, for which an individualised approach is useful in the attempt to find the best drug at the best dose, combining adequate clinical response with the lowest number of adverse effects. In the choice of an antidepressant, it is thus necessary to consider factors related to treatment (efficacy, tolerability, safety, formula-

TABLE II.
Adverse effects of the main antidepressants (adapted from http://tmedweb.tulane.edu/pharmwiki/doku.php/antidepressant_side_effects).

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QTC	Gastrointestinal toxicity	Weight gain	Sexual dysfunction
SSRI								
Citalopram	0	0	1+	1+	1+	1+	1+	3+
Escitalopram	0	0	1+	1+	1+	1+	1+	3+
Fluoxetine	0	0	2+	1+	1+	1+	1+	3+
Fluvoxamine	0	1+	1+	1+	0-1+	1+	1+	3+
Paroxetine	1+	1+	1+	2+	0-1+	1+	2+	4+
Sertraline	0	0	2+	1+	0-1+	2+	1+	3+
SNRI								
Duloxetine	0	0	2+	0	0	2+	0	3+
Venlafaxine	0	1+	2+	0	1+	2+	0	3+
Atypical antidepressants								
Bupropion	0	0	2+	0	1+	1+	0	0
Mirtazapine	1+	4+	0	0	1+	0	4+	1+
Serotonin modulators								
Trazodone	0	4+	0	3+	2+	3+	1+	1+

Other strategies to treat depression, especially treatment-resistant depression, include electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagal nerve stimulation (VNS) and deep brain stimulation (DBS).

tion, costs, availability) and the patient (clinical picture, somatic comorbidities, individual response and tolerability, previous response to therapy).

For initial treatment, a drug must be chosen that can be tolerated by the patient and that allows achieving a therapeutic dose with good adherence to therapy; the role of the GP is important in informing the patient about possible adverse effects and adequately communication with patients so that therapy will not be interrupted. It also minimises patient distrust of pharmacological treatment. Initial improvement of symptoms can be observed at 2-4 weeks after therapy is initiated; the patient must understand that effects are not immediate. Before considering a treatment inefficacious, a trial period of 6-12 weeks should be used.

While behaviour towards the use of drugs is measurable, since data is available (number of prescriptions, consumption, costs), it is more difficult to analyse the "prescribing" behaviour of psychotherapeutic treatment. As outlined in the following paragraphs, guidelines emphasise the use of psychotherapy in treatment of patients with depression and anxiety disorders; both specialists and GPs need to keep several considerations in mind:

- accessibility to psychotherapy within the healthcare system is limited and therefore the patient's willingness to bear costs will affects its use;
- "psychotherapy" does not exist, but rather a series of psychotherapeutic approaches that are specific for treatment of various disorders; the wide range available creates confusion for GPs about the correct approach;
- from the above considerations, such approaches may be underutilised and/or used incorrectly, exposing the patient to failure to achieve therapeutic goals, in addition to sustaining economic costs.

It is therefore desirable that in the future a more codified and collaborative care model can be adopted where the GP, psychiatric specialist and psychotherapist share the information needed to establish the correct course of treatment to reduce 'split care', which reduces the efficacy of treatment.

The psychotherapies that can be used for treatment of depression include:

- cognitive behavioural therapy (CBT);
- interpersonal psychotherapy;
- family and couple therapy;
- psychodynamic psychotherapy;
- supportive psychotherapy.

Although scientific studies have shown small differences in the effectiveness of different approaches for treatment of unipolar depression [8], CBT and interpersonal psychotherapy are most frequently used in the initial therapy of mild to moderate depression, as they represent the most widely studied and effective. Compared to pharmacological therapy, psychotherapy has been shown to be comparable in reducing the symptoms of depression [9]. CBT aims to help patients identify recurring thoughts and dysfunctional patterns of reasoning and interpretation of reality in order to replace and/or supplement them with more functional beliefs.

In cases of severe depression at significant risk of suicide, self-harm, or self-neglect, the therapeutic course should consider referral by the GP to a psychiatric specialist; such cases may require hospitalisation. Concern-

FIGURE 1.
Considerations in patients who do not respond to antidepressant therapy (from Nemeroff, 2007, mod.) [10].

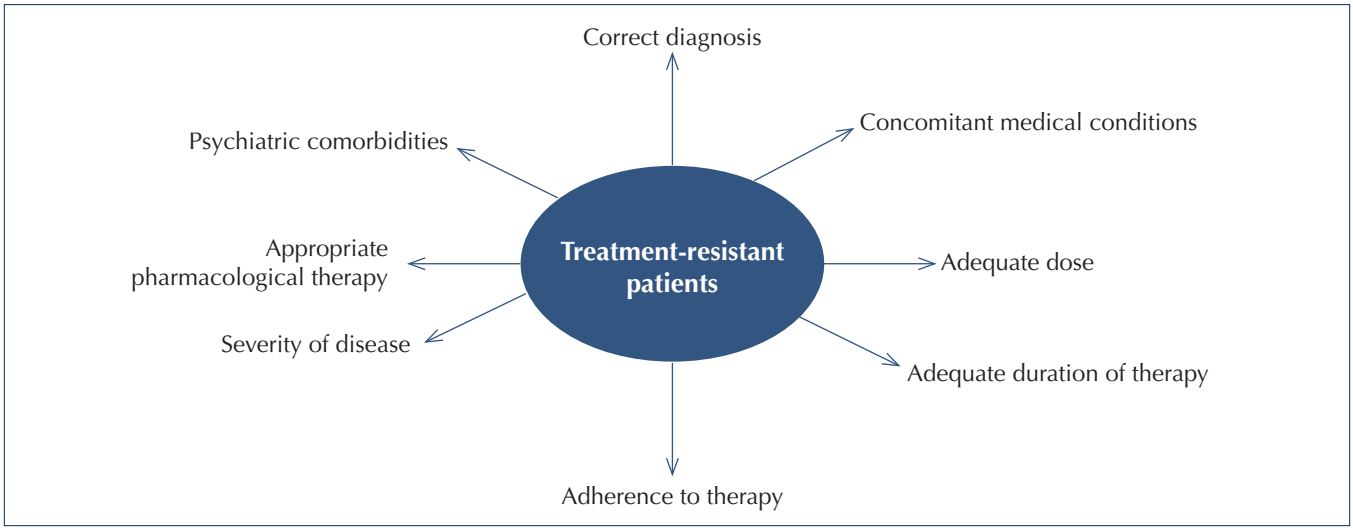


TABLE III.
Potential advantages and disadvantages of the main drug classes in clinical use.

	Advantages	Disadvantages
Tricyclic antidepressants	High clinical efficacy (reuptake of serotonin and/or norepinephrine)	Increased incidence of side effects (interaction with β-adrenergic, muscarinic and histamine H1 receptors)
Antidepressant SSRI	Particularly effective on psychic symptoms; reduce any anxious concomitant depressive symptoms; low potential for abuse	Less effective on somatic symptoms; variability in patient response; delay in onset of action; sexual dysfunction; weight gain; withdrawal symptoms; drug interactions (CYP 2D6)
Antidepressant SNRI	Broad spectrum of therapeutic activity Safety: reduced risk of toxicity in overdose Tolerability: less incidence of discontinuation for side effects	Related to activity of serotonin receptors: • gastrointestinal disturbances (nausea, vomiting, weight loss) • headache • sexual dysfunction (anorgasmia, decreased libido) • anxiety, tremor, nervousness, agitation • physical dependence "discontinuation syndrome" Related to noradrenergic receptor activity: • hypertension (at high dose
Trazodone	Anxiolytic and antidepressant efficacy with sedative effects (improved sleep); few anticholinergic effects; minimal sexual side effects	Orthostatic hypotension; sedation (sleepiness); cardiovascular problems: interaction with antihypertensives (may facilitate onset of hypotension and CNS depressant effects, e.g. clonidine); ventricular arrhythmias and torsades de pointes
Bupropion	Effective on lethargy, fatigue, apathy, drowsiness, reduction of interest and anhedonia Minimal effects on body weight and sexual function	Initial increase in anxiety levels; lowers threshold seizure
Mirtazapine	Improved sleep; no agitation, no sexual side effects, no nausea, no headaches	Increased weight gain
Agomelatine	Increases release of dopamine and norepinephrine but not 5-HT in the frontal cortex, with favourable effects on restoration of correct circadian rhythm	Possible worsening of liver function tests
Benzodiazepine	Especially effective for somatic symptoms; rapid onset of action; reproducible response and good tolerability	Less effective in psychological symptoms; possible addiction with the use of high long-term dosages; cognitive and psychomotor impairment; drug interactions (CYP 3A4)

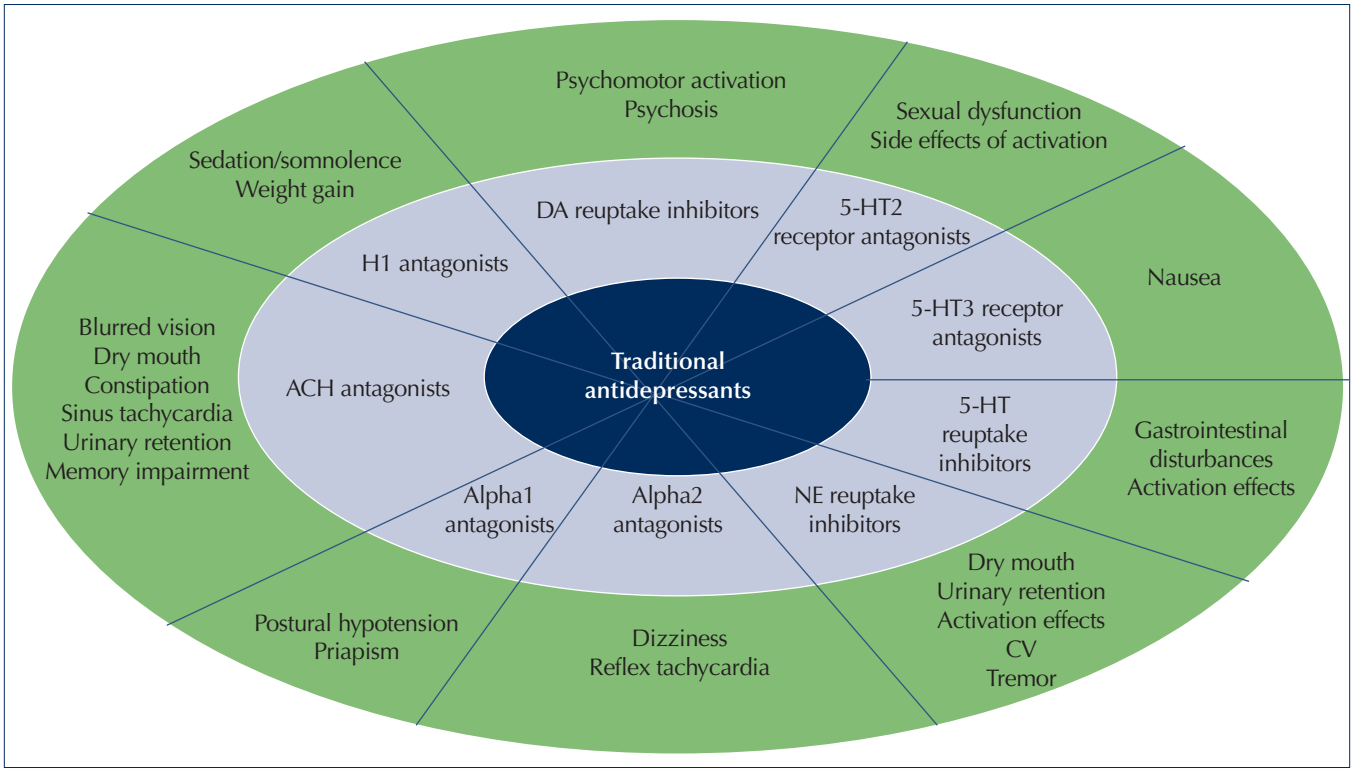
ing long-term treatment, the following should always be considered:

- a single episode of depression should be treated for at least 6-9 months after remission;
- the risk of recurrence of depression increases after each episode;
- patients suffering from several episodes require maintenance treatment for many years.

Patients with depression who present with significant anxiety symptoms are common in clinical practice; some studies have reported the co-presence of anxiety and depression in > 50% of patients. Treatment of patients with comorbid anxiety and depression includes the use of anxiolytics to control symptoms; in the acute phase of depression with significant anxiety symptoms, antidepressants have been shown to be less efficacious in this subgroup and, in some cases, anxiety symptoms can worsen during the first few weeks of treatment with antidepressants. Concomitant administration of anxiolytics and antidepressants should not continue for more than 4 weeks; after this initial phase of treatment, the anxiolytic should be tapered gradually and slowly for at least 2-4 weeks before discontinuation.

The use of combined therapies with a BDZ can rapidly improve anxiety symptoms, and also reduces the possible effects related to initiation of antidepressant therapy. Nonetheless, it is important to remember that the use of BDZs is associated with possible risks such as loss of efficacy over time (tolerance), sedation, psychomotor impairment and increased risk of falling (especially in elderly). BDZs should also be used with extreme caution in patients with a history of addiction (alcohol and/or sub-

FIGURE 2.
Side effects (adapted from Racagni G, Popoli M. Int Clin Psychopharmacol 2010;25:117-31).



stance abuse) and a history of difficult adherence to antidepressant therapy: both categories of patients are at risk of discontinuing the antidepressant and only continuing treatment with the BDZ, since it has a faster onset of action. The use of on-demand BDZs is not recommended: such an approach does not appear to be effective from a therapeutic standpoint; repeated access to a rescue dose can reinforce psychological dependence on the drug.

Several aspects should be considered in patients with panic disorder:

- the initial dose of an SSRI corresponds to half of the initial dose used for major depression and gradual titration is highly recommended to reduce the possibility of exacerbation of symptoms in the first days of therapy, in consideration of the greater sensitivity of these patients to the stimulating effects of SSRIs [11];
- the use of a BDZ should be considered in the first weeks of therapy to achieve rapid improvement of symptoms (the clinical benefits of an SSRI alone are obtained in 4-6 weeks), and to minimise possible side effects of initiation of therapy with an SSRI.

In patients who complain of insomnia, drug treatment is an effective and economical approach to treat a large number of patients. BDZs have demonstrated efficacy on insomnia, reducing latency and increasing the total sleep time. BDZs are not all equal as they have different affinities for the different subpopulations of receptors and different half-lives; all have the same dose-dependent effects (anxiolytic action, hypnotic-sedative, muscle relaxant, anticonvulsant). The choice between various BDZs depends primarily on the type of insomnia to be treated (initial, middle, end). When indicated, it is preferable to use a short or intermediate half-life BDZ to reduce the possibility of adverse events and complications, such psychomotor functions and daytime sedation.

In insomnia associated with depression, therapeutic intervention may include the use of antidepressants associated with hypnotic drugs, with varying effectiveness depending on the severity of depression and type of insomnia. Antidepressants can have a positive effect on insomnia during the course of depression or may have an "activating" effect that disturbs sleep. Some SSRI and SNRI antidepressants can disrupt sleep; in order to minimise effects on sleep the dose should be taken in the morning and at an antidepressant dosage.

Take-home messages

- Pharmacological therapy with antidepressants alone, psychotherapy alone, or a combination of both treat-

ments are efficacious in treatment of depression, generalised anxiety disorder, panic attacks and insomnia.
- The choice of treatment should take into account patient preferences and should be decided together with the patient.
- It is important to involve the patient in the therapeutic process through adequate communication that informs the patient, especially regarding the time to therapeutic response after the start of treatment (pharmacological and/or psychotherapeutic) and possible onset of common adverse effects when an antidepressant is used.
- SSRIs and SNRIs are the first choice for treatment of depression and have demonstrated efficacy and safety even when used in the setting of general medicine.
- It is recommended to use the lowest effective therapeutic dose of an SSRI or SNRI at the beginning of therapy for depression. Initial improvement begins at 4 weeks after the initiation of therapy.
- In panic attack disorder, the starting dose of an SSRI or SNRI is one-half that normally used in treatment of depression, and should be gradually titrated over 2-4 weeks.
- A BDZ can be used in the first 4 weeks of therapy for depression in the presence of significant anxiety symptoms, in panic attack disorder and insomnia in order to achieve rapid improvement in symptoms.

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Antidepressants and compliance

A. Rossi

Introduction

Compliance is defined as the extent to which the behaviour of a person, in terms of taking medication or lifestyle changes, corresponds to a medical prescription [1]. Therefore, compliance should not be understood simply as "lack of taking a medication", since it involves a wide range of behavioural and lifestyles changes, each of which plays an important role in the overall success of treatment. As a result, unsatisfactory compliance can be related to failure to comply with outpatient visits, not performing monitoring tests, early treatment discontinuation, or rejection or modification of the prescribed treatment [2].

For a more interactive, collaborative and proactive approach, many researchers and clinicians have suggested the use of the term 'adherence' or 'alliance', rather than 'compliance' [3]. However, at present, the terms adherence and compliance are used interchangeably. Traditionally, rates of discontinuation during treatment are considered the best index of non-adherence.

In the field of psychiatry, Cramer and Rosenheck [4] reported that adherence to pharmacological therapy in patients with psychiatric disorders is less than patients with physical diseases, with a rate of non-adherence in the former that varies from 24 to 90% with a mean level of non-adherence of around 60%. In particular, in treatment of depressive disorders compliance is important to achieve all the objectives of antidepressant therapy, which include resolution of symptoms, restore normal functioning and prevent relapses and recurrent episodes [5]. If therapy is adhered to, about 70% of patients with depression can be successfully treated by pharmacotherapy [6], but in spite of the availability of efficacious antidepressants, the rates of recurrence for depression

approaches 80% [7], and therapeutic failure is frequent, from 40 to 60% [8].
Moreover, guidelines for treatment of depression are not always followed and non-adherence rates are high, with 28% of patients discontinuing treatment with antidepressants within the first month and 44% discontinuing within three months after initiation of therapy. Bull et al. [9] have reported that up to 68% of patients with depression stop taking antidepressants after only three months of treatment.
In randomised clinical trials, discontinuation rates are between 20 and 40%, with the most frequent reason for discontinuation represented by "side effects", while in naturalistic studies the rates are higher, usually 50-60% within 10 weeks, with the category 'feel better' cited as the most frequent reason [10]. In addition, the overall rate of adherence decreases by 2.5% for each month of treatment with antidepressants, as reported Demyttenaere et al. (2008) [11].
In recent years, considerable progress has been made in the identification of risk factors of non-compliance to therapy with antidepressants and in developing strategies to assess and improve adherence, which can lead to better therapeutic results and decrease the morbidity of depressive disorders

How to assess compliance

Compliance to pharmacological therapy is usually classified as "good" (75-100% of doses), "average" (25-75% of doses), "poor" (0-25% of doses). "Hyper-compliance" is defined as the intake of >100% of doses. Such behaviour is often established by the patient in the belief that this will accelerate the onset of action or increase its effectiveness [12]. Leite et al. [13] stated that adherence to treatment should be defined as use of the prescribed medication for at least 80% of the time, taking into account time of day, dosage and total duration of treatment.
Quantifying non-compliance and its consequences is not straightforward. Demyttenaere [12] identified two methodological problems: the first is inherent to the reliability of study results, while the second involves the instruments used. The author holds that compliance is greater in clinical studies than in clinical practice, and that it is even greater in clinical studies that investigate adhesion to therapy. It was also stated that, in the field of adherence to therapy, simple measurement tools are not accurate, and accurate ones are not easy to use.
According to Farmer, tools to measure adherence to pharmacological therapy can be divided into direct and indirect [14]. The first provide evidence that the patient has taken the drug and include: detection of the drug or its metabolite in a biological fluid (usually blood or urine), detection of a biological marker co-administered with the drug (or placebo) and direct patient observation. The presence of a drug or its metabolite in a biological fluid provides confirmation that the patient has received a dose of medication within a certain period before testing. The presence of the drug in a test, however, does not ensure good compliance, and its absence does not always correspond to non-compliance. Most patients may have similar serum levels of the target drug, but may have taken the drug in a different way; serum or urine levels cannot quantify the mode in which the patient has taken the drug or detect fluctuations of compliance over time. Finally, inter-individual variations in metabolism and in the volume of distribution influence the level of medication regardless of adherence, making it hard to measure. Biological markers are non-toxic, stable compounds that are easily identifiable, which can be added to the drug to be monitored; they provide qualitative evidence that the patient has recently received a dose of drug. Lastly, in closely monitored clinical trials patients can be observed directly while taking the drug. This method is not always applicable or infallible as patients can deliberately pretend to swallow the medication.
The majority of the assessment methods used, however, are indirect and include self-reporting by the patient, counting of tablets, revision of the prescription registers and electronic monitoring devices.
Accounts given by patients on how they take medication is the easiest means of evaluating compliance. Patient interviews are generally considered to be a reliable method, even if the method of self-report used and the way in which it is used must be considered, given that patient responses may be influenced by both communication with the physician and the specific wording of questions. Several researchers have tried to correct such shortcomings by developing standardised self-report questionnaires to measure adherence to a treatment regimen, including the Morisky-Green test (MGT) [15] and Brief Medication Questionnaire (BMQ) [16].
For patients with depressive disorder, Demyttenaere et al. [17] developed the Antidepressant Compliance Questionnaire (ADCQ), which evaluates attitudes and beliefs of patients about depression and treatment with antidepressants. Finally, Gabriel and Violato [18] developed the Antidepressant Adherence Scale (AAS), which queries the patient's knowledge and attitudes towards depressive disorder as determinants of compliance.
Counting tablets involves simple counting of the number of doses that the patient has not taken, and comparing the doses given to those prescribed. In recent years, the use of computerised prescription records has increased utilisation of prescription adjustments, which allow researchers to investigate early discon-

tinuation of therapy and taking medicines in ways that it was not prescribed.
Finally, electronic monitoring devices, including the Medication Event Monitoring System (MEMS), contain a microprocessor that records the time and date on which the patient receives a dose of the drug. They are useful as they allow one to identify the voluntary deviations from the prescribed regimen and the effect of daily distribution of doses.
George et al. [19] compared four different methods for evaluation of compliance to determine the advantages and disadvantages. The following were used: patient self-report, counting tablets, MEMS and plasma assays of dothiepin and nordothiepin. The techniques were evaluated in 88 patients who initiated treatment with a tricyclic antidepressant in a GP setting. MEMS was the most informative technique and was considered to be the 'gold standard'. The Morisky questionnaire was found to be a useful screening technique with a sensitivity between 72 and 84% for identification of low compliance and a specificity of 74.1% for good compliance (> 80%). As in previous studies, pill count was difficult and of questionable validity. Of the four methods, the least satisfactory was measurement of blood concentration.

Factors that influence compliance

Adherence to antidepressant treatment is influenced by multidimensional factors. In agreement with most literature data, the aforementioned study by Demyttenaere et al. [10] showed that the most frequently reported reasons for discontinuation of therapy by patients are "feel better" (55%, average time of discontinuation 11 weeks) and appearance of side effects (23%, average time 6.5 weeks). However, several reasons were responsible for the discontinuation at different times over the course of the study.
The main factors influencing adherence are related to the characteristics of the disease, the patient, treatment and the doctor-patient relationship. Chronic, asymptomatic diseases that require long-term treatment, such as depressive disorder, are associated with lower compliance: the longer the remission phase, the lower compliance to therapy [20]. In addition, diseases in which the relationship between non-compliance and relapse is clear (e.g. diabetes) are associated with better compliance than those in which the relationship is less clear (e.g. depressive disorder) [21]. Demyttenaere [11] highlighted that depression in itself can passively reduce adherence. In fact, patients often have memory problems, and may feel hopeless and have less motivation. Ayalon et al. [22], in a study of elderly patients, noted that interruption of treatment, and in particular unintentional interruption, is associated mainly with the presence of more pronounced cognitive deficits. Furthermore, cognitive impairment can also affect patient insight. Lee et al. [23] examined the role of insight and adherence and showed that patients with more severe depression tend to have a greater insight, but that the latter is not associated with better adherence. Many studies have investigated the correlation between patient demographics and compliance. Despite the general assumption that older patients are less compliant than younger individuals, this relationship is not yet firmly established [24], and it seems that other related features, such as old age, social isolation and polypharmacy, are predictive of lower compliance. The notion that older patients are less compliant is supported by a study by van Geffen et al. [25] in which interruption of treatment was twice as high in patients 60 years and older.
In contrast, Brown et al. [26] reported that older patients are more adherent to therapy than younger patients. Looking in detail at the results of van Geffen et al. [25] and Brown et al. [26], it would seem, however, that older patients were more likely to question the use of drug therapy before trying it, whereas they may be more motivated to stay on therapy once it is initiated. Demyttenaere [11] found that non-compliance is higher in women than in men [11] and, similarly, Brown et al. [26] observed that men are more compliant women.
Kessing et al. [27] investigated the attitudes and beliefs of depressed bipolar patients and towards antidepressants. They reported that a large number of patients, especially those over 40 years, generally had a negative view of antidepressants, unclear ideas regarding their influence and a critical vision of the doctor-patient relationship.
Even personality-related aspects are important predictors of compliance, and their identification can help in developing individualised treatment regimens. In 2004, Cohen et al. [28] investigated the relationship between personality characteristics, according to a 5-factor model, and compliance to antidepressant treatment in 65 outpatients with major depressive disorder. They reported that extroversion was a significant negative predictor of compliance, while the subdomain modesty was a positive predictor. In the same study, the authors showed that none of the socio-demographic or disease-related characteristics such as age, sex, or number of previous depressive episodes, correlated with compliance.
Another interesting aspect is the type of pharmacological treatment that the patient receives and, above all, its dosage. Shigemura et al. [29], in a study on 1151 subjects with major depressive disorder, observed that patients with daily monotherapy had greater adherence compared with bid or tid dosing, suggesting that a reduction in the frequency of administration improves

adherence. The class of antidepressants had no significant effect on adherence.
Even the formulation may affect compliance. The currently available antidepressants are typically formulated as tablets or capsules for oral administration; in some cases they are also available as an oral suspension and intravenous formulation. However, extended release formulations of fluoxetine, venlafaxine, bupropion and paroxetine are under development, which offer greater ease of use and improved adherence [30-32]. Regarding the visual characteristics of the drug (e.g. form, size and colour), de Craen et al. [33] found that red, orange and yellow tablets are most appropriate for stimulant drugs, and that blue and green are better suited for sedatives. Buckalew et al. [34] reported that capsules are perceived as being more powerful than tablets and that the size of the capsule corresponds to perception of efficacy. In many studies, the appearance of side effects was a key cause of treatment discontinuation.
In an investigation by Bull et al. [35], 43% of patients who discontinued treatment within 3 months did so because of side effects. This proportion decreased to 27% in the second quarter of treatment, suggesting that patients who interrupt for side effects are more likely to do so at an early stage of therapy. Ashton et al. [36], even if they found that lack of efficacy was the most common reason for interruption, also stressed the central role of side effects, including loss of sexual interest, fatigue and lethargy, and significant weight gain.
Regarding the influence of the drug class on compliance, data in the literature have given as much consideration to effectiveness as to side effects of the two major classes of antidepressants currently in use (SSRIs and TCA). A meta-analysis [37] of 102 randomised controlled clinical trials of SSRIs and TCAs found no significant differences in efficacy between the two classes. However, although significant differences were seen in discontinuation rates, the clinical relevance of such differences is unclear. Discontinuation rates between the two classes are similar, although SSRIs have a better tolerability profile.
Bull et al. [35] studied doctor-patient communication. Considering the availability of many well-tolerated antidepressants, the authors found that the rate of treatment interruption cannot be explained solely by the appearance of side effects. Both physicians and patients compiled a questionnaire about the information that had been given to the patient on the antidepressant and duration of treatment. Interestingly, 72% of doctors referred that they had advised the patient to continue treatment for at least 6 months. In contrast, only 34% of patients remembered receiving such advice. The percentage of non-compliance was three times greater for patients who thought they were not informed. Moreover, if the possible side effects of the drug had been discussed, patients were more likely to continue therapy. These results clearly highlight the importance of the doctor-patient relationship in adherence to therapy.
More recently, Tamburrino et al. [38] found that patients who are not satisfied with their physician tend to be less compliant, and especially among those who have felt that they had not been adequately informed about the side effects of treatment. Similar results were found in the study by Brown et al. [26], who reported that it is beneficial for physicians to discuss the possible side effects with patients and inform them about how to take their therapy. In general, patients who are very satisfied with their physician are more compliant [29].

How to improve compliance

Adequate education and active participation are fundamental to improve adherence during treatment in patients with depressive disorder. Interventions that target the patient, the physician and the structural aspects of care can potentially improve adherence and treatment outcomes. If the patient is well informed about the course of the disease, symptoms and prognosis, adherence is better.
Several strategies have been developed to improve compliance, including: improving communication, patient education, dose optimisation and scheduling of follow-up visits. To improve doctor-patient communication, Cramer [39] proposed that the physician should discuss diagnosis and treatment with the patient, as well as the therapeutic plan chosen and timing of follow-up. Education should include information about treatment and healthcare providers should offer supportive interventions to patients and family members, while the treatment regimen should include reduction in the number of daily doses and number of drugs taken.
Even the problem of generic prescriptions may interfere with adhesion and should be discussed with the patient [40]. As early as 1997, Demyttenaere 12 highlighted the importance of the doctor-patient relationship in this regard, stating that patients who perceive the physician as empathetic and disposed to diminish their worries are more compliant. In the previously-mentioned study by Ashton et al. [36], the authors concluded that compliance can be promoted through better understanding of the expectations and desires of patients to therapy and by prescription of antidepressants associated with a low incidence of side effects.
Finally, in a systematic review assessing the effectiveness of interventions to improve compliance, Vergouwen et al. [41] noted that collaborative care interventions, tested in primary care settings, have shown significant improve-

ments in adherence during the acute and maintenance phases of treatment, and were associated with clinical benefit, especially in patients with major depression who were prescribed suboptimal doses of drugs. In the same meta-analysis, however, the evidence did not confirm the utility of educational interventions.

Conflict of interest
None.

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