Chapter 1

Current depression landscape: a state of the field today

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Abstract

More than two dozen pharmacological treatments are currently available for depression, working by more than a half dozen mechanisms, yet there remain many unmet therapeutic needs. Available antidepressants act directly on monoamine mechanisms, influencing receptors and transporters for serotonin, norepinephrine, and/or dopamine. Truly novel therapeutic targets beyond the monoamines have not emerged in the past few decades. Advances have been mostly in improved tolerability, and as a result, limitations in efficacy persist for all agents in the antidepressant class. Specifically, far too few patients, perhaps only a third, attain a full remission of symptoms, and those who have had many episodes of depression are not likely to sustain any remission for more than a few months. Thus, there is the urgent need for antidepressants with improved efficacy. Although the "holy grail" of antidepressant treatment has long been rapid onset of action, the reality is that more robust and sustained efficacy, even if delayed, is the unmet need of today. This is unlikely to be met by targeting the same monoamine transporters and receptors where current antidepressants act, so novel therapeutic targets must be identified if there is to be novel therapeutic efficacy of more robust and sustained antidepressant action.

Other issues in the treatment of depression include the increasing confusion between unipolar and bipolar depression, particularly at onset of first depressive episodes, as well as the confusion between treatment-resistant unipolar depression versus difficult-to-treat rapid cycling, mixed episodes of bipolar depression. Treatments for bipolar depression such as anticonvulsants and atypical antipsychotics are increasingly being used for bipolar and treatment-resistant cases. Future therapeutics may usefully exploit these mechanisms, and treatment of difficult cases in the future will likely involve use of multiple simultaneous mechanisms, either with multiple drugs or with multifunctional drugs.

There is also concern that depression may be a progressive illness, with unipolar depression progressing to treatment-resistant depression or even to bipolar spectrum disorder, and bipolar disorder progressing to rapid cycling and mixed treatment-resistant bipolar episodes. Future treatments of depression may not only have the potential to treat current symptoms and prevent their relapse, but also to halt progression and thus be disease-modifying, altering the course of untreated or inadequately treated illness.

At the beginning there were three monoamines . . .

The World Health Organization estimates that depression is the fourth leading cause of disability worldwide, with a lifetime prevalence of about 15–20% [1]. The first reports of antidepressant treatments date back to the early 1950s, when researchers in the United States

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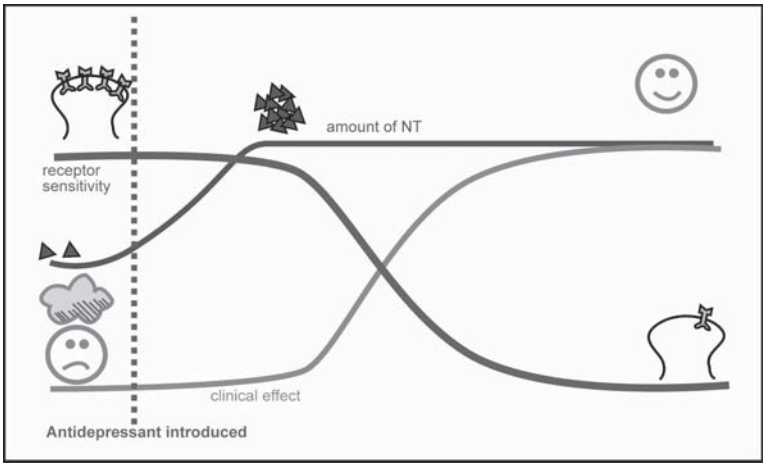

Figure 1.1 Time course of antidepressant effects. Depicted here is the time course for (1) clinical changes, (2) neurotransmitter changes, and (3) receptor sensitivity changes following antidepressant treatment. The amount of neurotransmitter changes rapidly following the introduction of an antidepressant. The clinical effect, however, is delayed, as is the downregulation of neurotransmitter receptors. The temporal correlation between the changes in clinical effect and the changes in receptor sensitivity has prompted researchers to posit the hypothesis that changes in neurotransmitter receptor sensitivity may actually induce the clinical effects of antidepressant medications. Besides the antidepressant and anxiolytic actions, these clinical effects also include tolerance to the acute side effects of these medications.

and in Europe simultaneously reported that two antituberculosis agents, isonazid and iproniazid, had mood-enhancing properties in patients [2,3]. It was not until the late 1950s that an opportune discovery of mood-enhancing effects of tricyclic (three rings) drugs led to the first antidepressant. Unfortunately, at the time, the number of people diagnosed with depression who would benefit from these "new" drugs remained low (50–100 per million), so this was not the top priority of the pharmaceutical companies [4]. The big blockbuster drug for depression only hit the market in 1988, when the Food and Drug Administration approved the first selective serotonin reuptake inhibitor (SSRI), fluoxetine. This "legitimized" depression as an important disorder for the pharmaceutical industry to investigate and develop better pharmacotherapies for.

Based on the monoamine hypothesis of depression, which posits a lack in monoamines in various brain regions of depressed patients, the development of antidepressant medications has focused on increasing the levels and synaptic effects of three monoamines: the catecholamines dopamine and norepinephrine, and the indoleamine serotonin [5]. The mechanism of action by which an increase in monoamines is generated often includes blockade of the various transporters for these monoamines, namely the dopamine transporter (DAT), the norepinephrine transporter (NET), and the serotonin transporter (SERT). However, the monoamine levels can increase quite rapidly following blockade of these transporters, while the clinical benefits of antidepressants often lag behind this effect by weeks. The neurotransmitter receptor sensitivity hypothesis of depression can explain this lag time, and is in line with the neurotransmitter receptor hypothesis that focuses on the abnormal upregulation of receptors in depression. By elevating neurotransmitter levels for an extended period of time, antidepressants can lead to the downregulation of the pathologic receptor upregulation. This is consistent with the time required to obtain clinical efficacy upon initiation of antidepressant treatment (Figure 1.1).

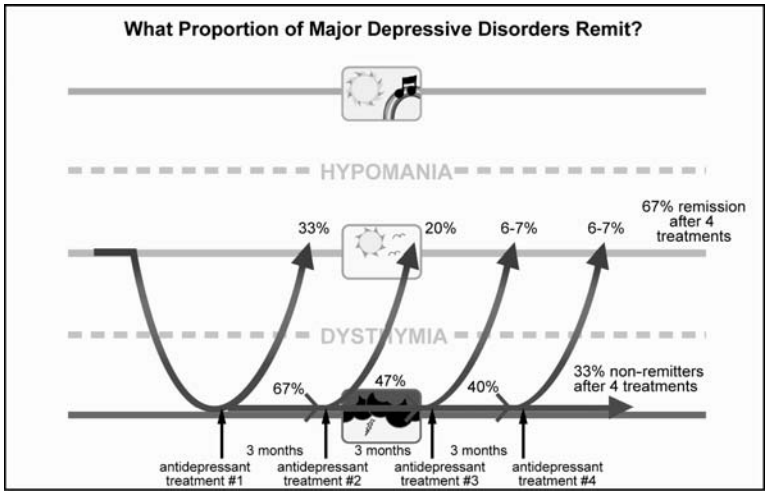

Figure 1.2 Remission rates in major depressive disorder. It has been estimated that one-third of patients with depression will remit during the first treatment with any antidepressant. For those who do not remit, the likelihood of remission with another antidepressant monotherapy decreases with each additional trial. After four sequential 12-week treatments only two-thirds of patients will have achieved full remission.

Of course, the changes in receptor number or sensitivity obtained following antidepressant effects certainly also require alterations in gene expression, transcription, and translation, and in the production of various neurotrophic factors. Preclinical studies have shown that brain-derived neurotrophic factor (BDNF) is one candidate whose expression levels are increased following antidepressant treatment [6]. Thus, besides modulating monoamine and receptor levels, the final common pathway to all antidepressants may be the regulation of various trophic factors.

STAR*D and treatment approaches

While many patients respond favorably to the antidepressants currently on the market, a significant number experience residual symptoms, treatment resistance, and relapse. The recent STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study [7] has shed some light on the reality of antidepressant treatment. Initially, only one-third of patients on citalopram monotherapy remitted. The other two-thirds who failed to remit saw their likelihood of remission decrease with each successive trial of another antidepressant monotherapy. Thus, after 4 successive monotherapies were tried for 12 weeks each, i.e. after one year of treatment, only two-thirds of patients achieved remission (Figure 1.2). Additionally, the more treatment cycles it took to get the patient to remit, the higher the likelihood of relapse.

The STAR*D results has sent a shockwave through the medical community, as it debunked previously held beliefs that major depressive disorder was highly treatable, and that some antidepressants were superior in efficacy to others. The results have also highlighted the need to further explore more effective treatment methods for major depressive disorder. New treatments are currently under development or have just hit the market, and these include new formulations of old antidepressants, new medications focusing on the monoamine hypothesis of depression, and experimental agents with novel mechanisms of action (see the section on improving treatments).

If multiple successive monotherapies with one antidepressant are not the way to effectively treat major depressive disorder, then what actions should be implemented to ascertain

Table 1.1 Stages of primary unipolar depression (adapted from [13]).

1. Prodromal phase (anxiety, irritable mood, anhedonia, sleep disorders)
   a. no depressive symptoms
   b. minor depression
2. Major depressive episode
3. Residual phase
   a. no depressive symptoms
   b. dysthymia
4. a. recurrent depression
   b. double depression
5. Chronic major depressive episode (lasting at least 2 years without interruptions)

maximum benefit to the patient? Some experts are suggesting that it may be beneficial to use augmentation and combination strategies from the outset of the first treatment in order to enhance the outcome of the treatment, namely remission. The synergistic effect of multiple medications combined with their broader spectrum of action may prevent the initiation of oppositional tolerance [8,9]. However, besides developing better pharmacological treatment approaches, the field of psychiatry may also want to borrow from general medicine, and adopt the "staging method" to properly diagnose the big picture of depression [10,11]. While the DSM-IV looks at depression as a flat, cross-sectional view of the patient's ailments, the "staging method" takes into account the longitudinal development of depression, including previous episodes and the response to previous treatments. Primary unipolar depression, for example, has been divided into five stages: a prodromal phase can lead to the major depressive episode which can result in a residual phase that can escalate into recurrent depression and finally chronic depressive episodes (see Table 1.1) [12].

While this type of staging of major depression may already occur behind a psychiatrist's door, its application may need to be expanded to all healthcare practitioners, as it could impact on the success of a pharmacological treatment as well. A medication that may be useful in one stage may be less efficacious in another; or psychosocial therapy in conjunction with pharmacotherapy may be more beneficial in severe versus chronic depression [13]. Thus it becomes important to adopt a holistic view when talking about diagnosis and treatment of major depressive disorder.

Improving treatments: "make-over" of old medications

In order to improve tolerability and thus adherence to medications, it may be necessary to further investigate different formulations of old medications. Recently, bupropion has been developed in a hydrobromide salt formulation instead of the traditional hydrochloride salt formulation. This allows for higher doses (mg equivalency to buproprion hydrochloride salt) to be packaged into one pill, therefore potentially facilitating higher dosing in treatment-resistant patients.

Trazodone is currently undergoing a "make over" and waiting for approval of its new high-dose (300–450 mg), once-daily controlled release formulation. This formulation would allow patients to take the necessary higher doses without experiencing the sedatory side effects the following day.

The active metabolite of venlaflaxine, desvenlaflaxine, is being "made over" into its own legitimate antidepressant. Being produced following enzymatic activity by CYP450 2D6, desvenlaflaxine is less metabolized than the mother compound and may thus allow for more stable plasma levels [14]. Like venlaflaxine, desvenlaflaxine is a more potent inhibitor of SERT than NET, but when compared to the same doses of venlaflaxine, desvenlaflaxine exhibits greater potency at NET than SERT. This property may render it a perfect candidate to treat painful and vasomotor symptoms, which are theoretically due to a malfunctioning NE system. Desvenlaflaxine is also efficacious at treating hot flushes associated with perimenopause, but due to cardiovascular safety concerns is not approved for such use [5,15].

Improving treatments: new ways to tweak monoamine levels

Atypical antipsychotics exhibit different degrees of success when treating the depressed phase of bipolar disorder [5]. This is most likely the result of their very elaborate receptor profile, as they can lead to increased levels of serotonin, norepinephrine, and dopamine, either directly or indirectly. Their mood-enhancing property can result from the direct blockade of NET thus increasing norepinephrine levels, or the direct blockade of SERT thus increasing serotonin levels. Indirect action via the alpha 2 receptors can lead to enhanced norepinephrine and serotonin levels, and modulation of various serotonin receptors including the 5HT2A, 5HT2C, and 5HT1A can, by disinhibiting norepinephrine and dopamine, indirectly result in increased levels of these monoamines.

As atypical antipsychotics are an eclectic mix of different compounds, they also treat the depressed phase of bipolar disorder with varying efficacy in different patients. Quetiapine appears to have the highest efficacy as monotherapy in the treatment of bipolar depression. At the correct doses, its active metabolite norquetiapine leads to just the appropriate mix of receptor modulation, namely less than full saturation of D2 receptors, proper inhibition of 5HT2C receptors and NET, and adequate stimulation of 5HT1A receptors [5,14]. One limitation as to whether these compounds will become mainstream in the treatment of unipolar depression may depend on their side effect and cost profile [16].

The search for the most efficacious antidepressant first took pharmacologists down the road of finding the most selective compound, such as the SSRI. Then pharmacologists developed compounds that selectively blocked two monoamines, for example serotonin and norepinephrine reuptake inhibitors. Today, the idea that a triple reuptake inhibitor may be the answer is gaining momentum. Table 1.2 lists different triple reuptake inhibitors, which target the serotonin, dopamine, and norepinephrine transporter with varying degrees. Full blockade of all three monoamine transporters is not optimal, and these compounds are trying to find the best balance that will lead to the most efficacious monoaminergic activity.

Another new group of compounds which have gained interest in the treatment of depression are the norepinephrine dopamine disinhibitors, or, simply stated, agents that block the 5HT2C receptors. The new antidepressant agomelatine, for example, is a potent 5HT2C blocker in addition to being an agonist at the melatonin 1 and 2 receptors; thus besides treating the symptoms of depression, it may be beneficial in improving sleep issues [14]. Table 1.3 lists the new agents in development that are targeting the different serotonin receptors.

Table 1.2 Triple reuptake inhibitors currently in development as antidepressants (table adapted from [17]).

Triple reuptake inhibitor	Additional receptor properties	Stage of development
DOV 216303		Phase II depression
DOV 21947		Phase II depression
GW 372475 (NS2359)		No ongoing clinical trials in depression; Phase II for attention deficit hyperactivity disorder
Boehringer/ NS2330		No ongoing clinical trials in depression; Phase II for Alzheimer dementia and for Parkinson's disease discontinued
NS2360		Preclinical
Sepracor SEP 225289		Phase II depression
Lu AA24530	5HT2C, 5HT3, 5HT2A, alpha 1A	Phase II depression
Lu AA37096	5HT6	Phase I
Lu AA34893	5HT2A, alpha 1A, and 5HT6	Phase II depression

Table 1.3 Serotonergic agents currently in development as antidepressants (table adapted from [17]).

New serotonergic targets	Agent	Additional receptor properties	Stage of development
5HT2C antagonism	Agomelatine	Melatonin 1 and 2	Approved EMEA with liver monitoring, Phase III depression in USA
SSRI/5HT3 antagonism	Lu AA21004	5HT1A	Phase III depression
SSRI/5HT1A partial agonism	Vilazodone (SB 659746A)		Phase III depression
5HT1A partial agonism	Gepirone ER		Late-stage development for depression
5HT1A partial agonism	PRX 00023		Phase II depression
5HT1A partial agonism	MN 305		No clinical trials in depression; Phase II/III for generalized anxiety disorder
Sigma 1/5HT1A partial agonism	VPI 013 (OPC 14523)	Serotonin transporter	Phase II depression
5HT1A agonism/ 5HT2A antagonism	TGW-00-AD/ AA		Phase II depression
SRI/5HT2/5HT1A/ 5HT1D	TGBA-01-AD		Phase II depression
5HT1B/D antagonism	Elzasonan		Phase II depression

Improving treatments: looking beyond the monoamines

While modulation of the three monoamines has had great success in the treatment of depression, it may be necessary to go beyond the monoamines to find newer, more efficacious drugs or better augmenting agents for difficult-to-treat or treatment-resistant depression. The medical food L-5-methyl-tetrahydrofolate (MTHF), a key derivative of folate, is an important player in the synthesis of monoamines, and if delivered directly to the brain can theoretically increase the levels of all monoamines [5], especially in patients who have not responded to previous antidepressant medications and who have low folate levels [18].

Table 1.4 lists a large number of novel agents with new targets that are either in preclinical or early clinical development [5]. These agents range from low-molecular-weight compounds acting at the hypothalamic–pituitary–adrenal axis to neurokinin receptor antagonists.

Thus, the search for the next antidepressant is certainly an interesting one, and can either build on properties already known to work or on new ideas that just may give us the "silver bullet" we are looking for.

Unipolar versus bipolar depression: are these present along a progressive mood disorder spectrum?

A major impediment regarding the adequate treatment of unipolar disorder has been the fact that a large proportion of patients initially diagnosed with unipolar depression actually have bipolar II disorder (Figure 1.3). Patients with bipolar II disorder spend more time in the depressed state than either the (hypo)manic or mixed states, and can be easily misdiagnosed with unipolar depression if a proper history is not taken. This unfortunately results in them being treated first with an antidepressant – which could lead to activation and mood cycling, and worse to suicidality – instead of receiving the proper treatment of lithium, an anticonvulsant mood stabilizer, or an atypical antipsychotic.

Successful recognition of whether a depressed patient has a bipolar disorder or unipolar depression lies in obtaining the proper family and medical history, as the symptoms the patient will present with are similar in unipolar versus bipolar depression (Figure 1.4). Patterns of past symptoms and the response to prior antidepressants, as well as current symptoms such as more time sleeping, overeating, comorbid anxiety, motor retardation, mood liability, or psychotic or suicidal thoughts can all be used to correctly discriminate unipolar depression from bipolar depression [5].

It also remains to be determined whether continuity exists between bipolar disorder and major depressive disorder. A review of the scientific literature suggests that a categorical approach may be best applicable when discussing the extremes of the mood spectrum, such as bipolar I and major depressive disorder, while midway disorders such as bipolar II and major depressive disorder plus bipolar signs should best be seen along a continuum or a spectrum [19]. Thus it is not yet clear whether all mood disorders should be placed on a spectrum, and therefore whether they should be treated using the same approach.

Another question that remains unanswered thus far is whether mood disorders such as unipolar depression and bipolar disorders are progressive (Figure 1.5). If unipolar depression is untreated or undertreated, will the presence of residual symptoms or even relapses lead to a deterioration of the illness accompanied by more frequent recurrences, shorter inter-episode recoveries and even potentially treatment resistance? Additionally, could this

Table 1.4 New compounds currently in development as antidepressants (table adapted from [17]).

New mechanism	Agent	Stage of development
Beta 3 agonism	Amibegron	Phase III discontinued
Neurokinin (NK) 2 antagonism	Saredutant (SR48968)	Phase III discontinued
NK2 antagonism	SAR 1022279	Preclinical
NK2 antagonism	SSR 241586 (NK2 and NK3)	Preclinical
NK2 antagonism	SR 144190	Phase I
NK2 antagonism	GR 159897	Preclinical
NK3 antagonism	Osanetant (SR142801)	No current clinical trials in depression; preliminary trials in schizophrenia
NK3 antagonism	Talnetant (SB223412)	No current clinical trials in depression; Phase II for schizophrenia and for irritable bowel syndrome
NK3 antagonism	SR 146977	Preclinical
Substance P antagonism	Aprepitant [MK869; L-754030 (Emend)]	Phase III discontinued
Substance P antagonism	L-758,298; L-829,165; L-733,060	No clinical trials in depression; Phase III for nausea/vomiting
Substance P antagonism	CP122721; CP99994; CP96345	Phase II depression
Substance P antagonism	Casopitant (GW679769)	No clinical trials in depression; Phase III for nausea/vomiting
Substance P antagonism	Vestipitant (GW 597599) +/– paroxetine	No clinical trials in depression; Phase II for social anxiety disorder
Substance P antagonism	LY 686017	No clinical trials in depression; Phase II for social anxiety disorder and for alcohol dependence/craving
Substance P antagonism	GW823296	Phase I
Substance P antagonism	(Nolpitantium) SR140333	No clinical trials in depression; Phase II for ulcerative colitis
Substance P antagonism	SSR240600; R-673	No clinical trials in depression; Phase II for overactive bladder
Substance P antagonism	NKP-608; AV608	No clinical trials in depression; Phase II for social anxiety disorder
Substance P antagonism	CGP49823	Preclinical
Substance P antagonism	SDZ NKT 34311	Preclinical
Substance P antagonism	SB679769	Preclinical
Substance P antagonism	GW597599	Phase II depression
Substance P antagonism	Vafopitant (GR205171)	No clinical trials in depression; Phase II for insomnia and for post-traumatic stress disorder
MIF-1 pentapeptide analog	Nemifitide (INN 00835)	Phase II depression – trial suspended
MIF-1 pentapeptide analog	5-Hydroxy-nemifitide (INN 01134)	Preclinical

Table 1.4 (cont.)

New mechanism	Agent	Stage of development
Glucocorticoid antagonism	Mifepristone (Corlux)	Phase III depression
Glucocorticoid antagonism	Org 34517; Org 34850 (glucocorticoid receptor II antagonists)	Phase III depression
corticotropin-releasing factor (CRF) 1 antagonism	R121919	Phase I
CRF1 antagonism	CP316,311	Phase II (trial terminated)
CRF1 antagonism	BMS 562086	Phase II
CRF1 antagonism	GW876008	No clinical trials in depression; Phase II for social anxiety disorder and for irritable bowel syndrome
CRF1 antagonism	ONO-233M	Preclinical
CRF1 antagonism	JNJ19567470; TS041	Preclinical
CRF1 antagonism	SSR125543	Phase I
CRF1 antagonism	SSR126374	Preclinical
Vasopressin 1B antagonism	SSR149415	Phase II

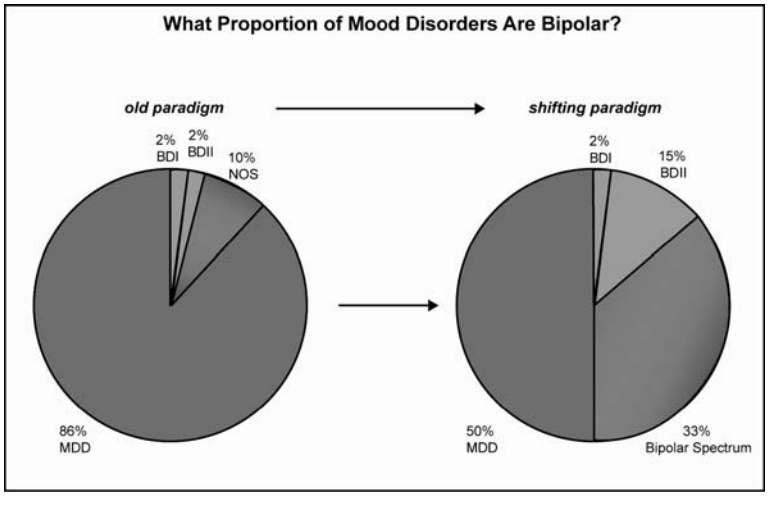

Figure 1.3 Incidence of mood disorders. Diagnoses of bipolar disorder (BD) have become increasingly common in recent years. Although many patients who would have previously been diagnosed with major depressive disorder (MOD) (old paradigm) are now being diagnosed with bipolar disorder (shifting paradigm), the syndrome can be hard to detect. There are still a large number of patients who go many years without an accurate diagnosis of bipolar disorder.

vicious circle of relapses lead to bipolar disorder? In the same line of thought, untreated or undertreated manic or depressive episodes could result in mixed and dysphoric episodes which could finally evolve into rapid cycling and treatment-resistant bipolar disorders. The balance between overdiagnosis and underdiagnosis of mood disorders is quite sensitive: is it

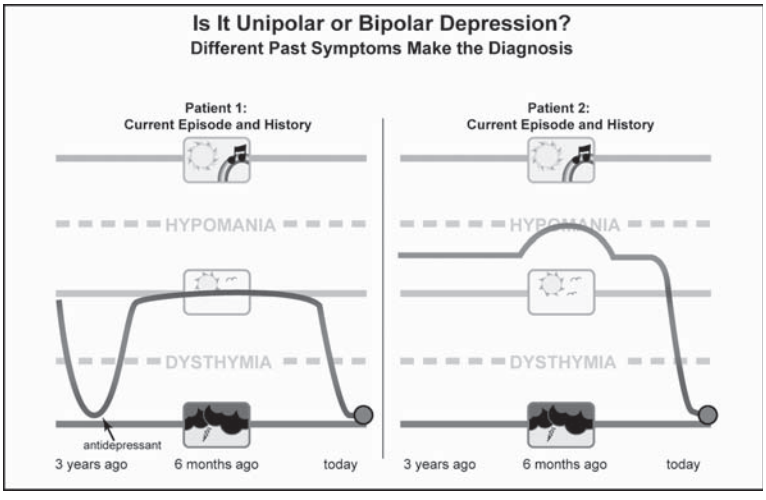

Figure 1.4 Unipolar versus bipolar depression. Both patients in this mood chart are "today" presenting with identical current symptoms of a major depressive episode (gray dot in the figure). Patient 1, however, has unipolar depression while patient 2 has bipolar depression. The pattern of past symptoms is relevant and can help distinguish between both disorders: patient 1 has experienced a prior depressive episode, while patient 2 has had a prior hypomanic episode. Gaining a complete picture may often require additional interviews with family members or close friends of the patient.

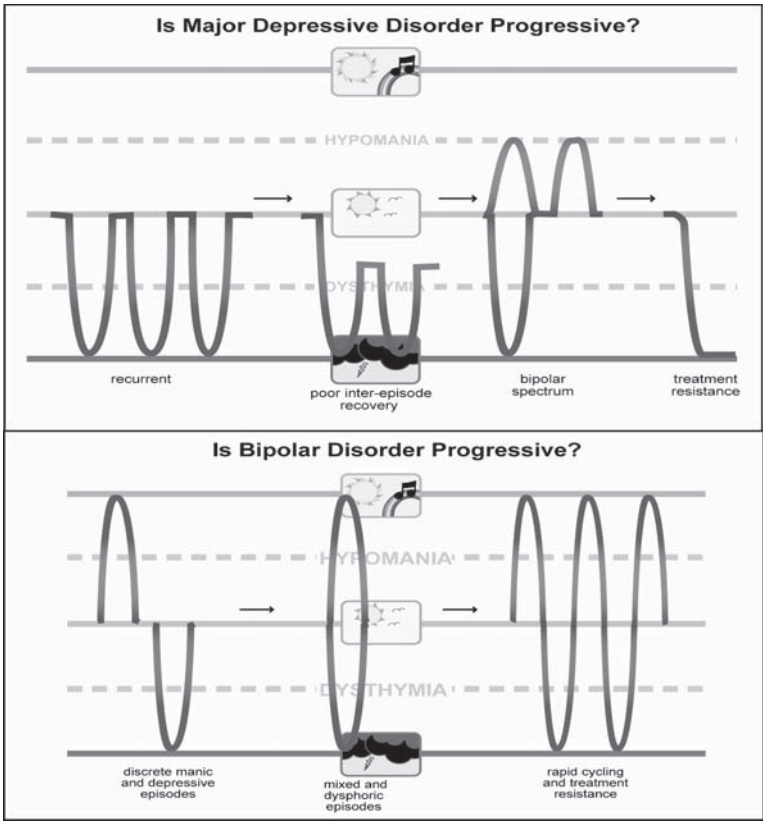

Figure 1.5 Are mood disorders progressive? (Top) It has been suggested that un(der)treated unipolar depression could develop into a bipolar spectrum condition, and could eventually reach the point of treatment resistance. (Bottom) It has further been posited that un(der) treated or mistreated episodes of mania and depression could develop into mixed or dysphoric episodes, rapid cycling and also finally into treatment resistance.