Rapid Onset of Antidepressant Action: A New Paradigm in the Research and Treatment of Major Depressive Disorder

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Objective: Current therapeutics of depression are similar in their time to antidepressant action and often take weeks to months to achieve response and remission, which commonly results in considerable morbidity and disruption in personal, professional, family, and social life, as well as risk for suicidal behavior. Thus, treatment strategies presenting a rapid improvement of depressive symptoms—within hours or even a few days—and whose effects are sustained would have an enormous impact on public health. This article reviews the published data related to different aspects of rapid improvement of depressive symptoms.

Data Sources: Literature for this review was obtained through a search of the MEDLINE database (1966–2007) using the following keywords and phrases: *rapid response, antidepressant, time to, glutamate, sleep, therapeutics, latency,* and *depression*. The data obtained were organized according to the following topics: clinical relevance and time course of antidepressant action, interventions showing evidence of rapid response and its potential neurobiological basis, and new technologies for better understanding rapid antidepressant actions.

Data Synthesis: A limited number of prospective studies evaluating rapid antidepressant actions have been conducted. Currently, only a few interventions have been shown to produce antidepressant response in hours or a few days. The neurobiological basis of these rapid antidepressant actions is only now being deciphered.

Conclusions: Certain experimental treatments can produce antidepressant response in a much shorter period of time than existing medications. Understanding the molecular basis of these experimental interventions is likely to lead to the development of improved therapeutics rather than simply furthering our knowledge of current standard antidepressants.

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Major depressive disorder (depression) is a severe, recurrent, and disabling medical illness that is highly prevalent worldwide and often associated with a negative impact on medical health, quality of life, and productivity.[1–3] Many factors influence clinical response and outcome in depression, including clinical presentation, comorbidities, past psychiatric and medical history, genetic makeup, and environmental factors.[4–7]

Several classes of antidepressants are currently used in the treatment of this devastating disorder. A delayed onset of antidepressant action is one of the major limitations of all existing antidepressant therapies despite their different pharmacologic profiles. For example, in the largest effectiveness study conducted to date in patients with unipolar depression, involving nearly 3000 outpatients, only 28% of patients treated with a standard antidepressant achieved remission within 10 to 14 weeks.[3,8] These findings suggest that full therapeutic effects usually take many weeks to manifest and, despite long-term treatment, a considerable number of patients still do not have satisfactory improvement. Furthermore, clinical improvement that occurs during the first few weeks of treatment with antidepressants seems to be a critical factor for achieving long-term clinical stability.[9] The potential role of early onset of antidepressant action as a surrogate endpoint for long-term sustained improvement seems to be associated with long-lasting benefits by limiting harmful neurobiological effects and poor outcome secondary to repeated depressive episodes and enduring depressive symptoms.[10–12]

Despite recent advances in the treatment of depression, reducing this delay in onset of antidepressant effects and improving the remission rates associated with existing treatments is a research goal that has not been sufficiently pursued. Thus, developing treatments with a rapid antidepressant action—especially a response or remission that occurs in a matter of hours or even a few days—could have an enormous impact on public health.

The aim of this article is to review studies on (1) time of onset of current antidepressant treatments, typically occurring within few weeks; (2) interventions leading to a significant improvement of core depressive symptoms within hours to a few days and presumed cellular mechanisms involved in the rapid onset of antidepressant actions; and (3) tools for better understanding rapid antidepressant actions. It is our hope that this article will stimulate new lines of drug development research on treatments that work within hours.

Literature for this review was obtained through a search of the MEDLINE database (1966–2007) using the following keywords and phrases: *rapid response, antidepressant, time to, glutamate, sleep, therapeutics, latency,* and *depression*. The data obtained were organized according to the following topics: clinical relevance and time course of antidepressant action, interventions showing evidence of rapid response and its potential neurobiological basis, and new technologies for better understanding rapid antidepressant actions.

RATIONALE FOR THE NEED OF RAPID ANTIDEPRESSANT ACTION: HIGH MORBIDITY DURING THE PERIOD OF LATENCY IN MAJOR DEPRESSIVE DISORDER

Standard antidepressants usually require approximately 1 month or more for antidepressant effects to manifest, and commonly, patients remain symptomatic and functionally impaired during this initial period of treatment.[13] Jick and colleagues[14] observed an increased risk of suicidal behavior during the first month of antidepressant treatment, particularly during the first 9 days; individuals showed similar rates of vulnerability regardless of the chemical class of their antidepressant. It is important to note that the higher risk of suicide and other deliberate acts of self-harm during the first month of treatment is not uncommon, and when it does occur has been postulated to be due to a mismatch in symptom improvement; that is, physical energy improves first, while resolution of depressive mood and negative thoughts (i.e., hopelessness and suicidal ideation) is more gradual. In support of this notion, Simon and colleagues[15] observed a significantly higher risk of suicide attempts during the first week of antidepressant treatment compared to later weeks. Another study[16] also described an increased risk for suicide attempt in the first month after starting antidepressant treatment. Teicher and colleagues[17] observed that the risk for this outcome was decreased in those depressed patients who had an earlier antidepressant response. Therefore, an earlier and sustained improvement in depressive symptoms would be expected to lead to an earlier restoration of functional well-being and productivity, sustained long-term remission, and a lower risk for a negative outcome.[18,19]

A delayed onset of antidepressant effects can also be associated with secondary psychosocial losses. It has been well documented that depression limits quality of life, thus impairing those skills necessary to work, to create and maintain relationships, to be productive, and to function in multiple other domains.[20,21] Consequently, severe depressive episodes should be characterized as an emergent condition that requires a rapidly effective intervention to limit the time spent in this state; such thinking is typically observed in many other medical disorders.

In recent years, rapid therapeutic effects have been shown to strongly modify the human and financial costs associated with many medical illnesses. For instance, triptans—which have been shown to produce maximum therapeutic effects for migraine within minutes or hours—have revolutionized the treatment of migraine. Since its release in 1991, sumatriptan has been used to treat over 200 million migrainous attacks by 10 million patients.[22] Interestingly, the primary endpoint usually measured in clinical trials of triptans for acute migraine therapy has been 2-hour pain relief, that is, a decrease in pain intensity from moderate/severe to mild/none.[23] Other examples of rapid therapeutic effects in medicine include the use of corticosteroids to treat asthma and intravenous verapamil or diltiazem to treat atrial fibrillation; both exert rapid therapeutic effects within minutes.

As a critical public health concern, these data strongly argue for the urgent need to research and develop new antidepressants that work rapidly to eliminate the early morbidity and mortality that result from depressive episodes.

TIME COURSE OF ANTIDEPRESSANT ACTION AND CLINICAL VARIABLES

Current Definitions

The timing of antidepressant response has been a well-debated topic in the psychiatric literature for the last twenty years. Although the common view is that standard antidepressants have a delayed onset of at least 2 weeks, this notion has been questioned by data from a number of large-scale studies and meta-analyses suggesting that some current antidepressant treatments can exert some initial beneficial effects within the first week.[7,19,24,25] However, other studies have suggested that the average time for onset of antidepressant action with standard antidepressants is around 2 weeks; when considering response criteria, this period goes up to 20 days.[26–28] Although the relevance of time course for antidepressant effects during

the first days of treatment in major depressive disorder is unequivocal, a number of methodological limitations are apparent in the study of this topic. For instance, the current definitions and rating scales used for the evaluation of antidepressant response/remission rates were developed to detect improvement only after 1 or more weeks based on weekly ratings and not improvement occurring within hours. Additionally, the methodological and statistical approaches for measuring this very early improvement may differ from those that have been in use. Finally, most of the findings about the early therapeutic effects of antidepressants come from post hoc analyses and meta-analyses of trials that were not specifically designed to detect the speed of antidepressant onset and are thus associated with several limitations.[29]

Treatment response has been widely characterized as a 50% decrease in depression compared to baseline, whereas the definition of remission is usually based on a lower threshold.[30,31] Some authors use the term to define remission as "full or total response." Conversely, there is no such general agreement about how to define "onset of improvement" in depression. Stassen and colleagues[26] defined onset of improvement as the initial moment when there is decrease of more than 20% from baseline without a subsequent increase. According to their meta-analysis, the estimated rate for early improvement (20%) predicted around 70% of those who responded at 4 weeks. Other investigators recommend using a 30% change from baseline to define a clinically meaningful improvement.[29] Similarly, Posternak and Zimmerman[24] defined onset of improvement as a sustained reduction of 20% to 33% in global symptom severity. The stringency of current criteria for evaluating rapid antidepressant effects and the lack of standard procedures for their measurement clearly demonstrate the need to test currently used depression rating scales according to different validity paradigms potentially associated with time course of improvement of depressive symptoms. Specifically, further evaluation of the optimal frequency for the application of rating scales and a clear definition of core symptoms associated with early improvement urgently need to be clarified.

Overall, current hypotheses on the potential mechanisms involved in antidepressant response only weakly address the observed interindividual variation in outcomes. Studies focusing on the onset of antidepressant effects may preferentially involve 2 major aspects. First, it will be critical to prospectively determine associations between the time needed for antidepressants to induce a significantly greater therapeutic effect in overall symptoms compared to placebo and other outcomes such as response and remission. Second, it will be key to determine the timing for improvement of individual depressive symptoms and constructs, based on findings showing that specific symptoms or groups of symptoms (clusters) may tend to remit faster than others and may generate clinically relevant predictors that directly associate with short- and long-term outcome. Variations between antidepressant classes in time to improvement of specific symptoms will be an important focus because they may point to differences in pharmacologic action.

The Timing of Antidepressant Onset Versus Placebo

Quitkin and colleagues[32,33] used a pattern analysis approach with 3 different trials and concluded that a real drug-placebo difference could occur only after 3 weeks of treatment. They emphasized that true drug responders present a delayed and sustained antidepressant onset and response, whereas placebo responders displayed early but not long-term sustained improvement. However, these conclusions have been questioned by a number of studies demonstrating early improvement (during the first 2 weeks) as a real antidepressant effect. Furthermore, this early therapeutic effect has the potential to predict a subsequent positive long-term outcome. A recent meta-analysis showed that patients using antidepressants had a significantly higher rate of sustained clinical response compared to placebo beginning at week 1 or 2.[25] Similarly, Posternak and Zimmerman[24] showed a significant, persistent difference in drug-placebo effect during the first 2 weeks in a meta-analysis of 5158 patients from 47 studies. Similarly, Tollefson and Holman[34] pooled the results from 6 trials and observed greater improvement in patients using fluoxetine compared to placebo that began in the first week. These studies provide an important impetus in furthering this line of research. Studies by Katz and colleagues[27,35,36] specifically designed to evaluate onset of antidepressant action are examples of this new effort to better understand the time course for achieving improvement of depressive symptoms. Thus, some antidepressants appear to exert initial therapeutic effects within the first 2 weeks.

Conversely, some limitations exist. First, although evidence supports this concept, the current data do not clearly define or standardize the concept of rapid antidepressant effects. Second, most of the studies pooled in the meta-analyses were not specifically designed to identify onset of improvement in terms of frequency of the assessments or statistical methods (see Statistical Issues in Evaluating Rapid Antidepressant Actions). Finally, the standard depression rating scales and subscales for evaluating onset of antidepressant action may be of limited utility when measuring score changes and differences between real antidepressant and placebo effects when assessments are made in less than a week, as would be the case when trying to assess early improvement.

The Timing for Improvement of Individual Depressive Symptoms and Constructs

Because depression is a multifaceted disorder, it has been proposed that any potentially valid outcome used

to evaluate rapid improvement of depressive symptoms should include application of specific subscales with cognitive, vegetative, and emotional dimensions.[29,35,37] In this context, Katz and colleagues[27,36] identified 11 depressive constructs using several rating scales during treatment with the antidepressants imipramine and amitriptyline. Some of these constructs, such as anxiety and depressed mood, were shown to significantly change during the first week of treatment in patients who had a therapeutic response to their antidepressant after 4 weeks of treatment.[36] In a subsequent placebo-controlled study, Katz and colleagues[27] compared possible changes in depressive constructs using antidepressants from 2 different chemical classes and found that 1 induced significant early improvement in 3 days. Interestingly, placebo responders had no specific behavioral pattern. Hirschfeld and colleagues[38] observed a significant difference between duloxetine (a serotonin and noradrenergic reuptake inhibitor) and placebo after 2 weeks of treatment. Patients taking duloxetine showed early improvement (within the first week) in a specific group of depressive symptoms.

Thus, the evaluation of early improvement in specific depressive symptoms and clusters may represent a true link between different constructs of depression and the pharmacologic action of diverse classes of antidepressants. For instance, paroxetine and desipramine may induce early improvement of specific symptoms and dimensions, thus challenging the common notion that different antidepressants exert the same clinical effects.[27] Also, the use of longer, standard, weekly scales to measure depression may sometimes mask real early improvements when lack of improvement in one set of symptoms drowns out changes in others.

The Relationship Between Early Antidepressant Effects and Long-Term Outcome

As mentioned above, several studies have demonstrated the influence of early improvement of depressive symptoms in predicting long-term outcome.[29,35,39–41] Post hoc analyses have shown that early improvement is highly predictive of response at study endpoint.[42] Montgomery[43] observed that patients showing an antidepressant onset after 10 days of treatment were more likely to achieve sustained response after 1 month. Katz and colleagues[27,44] suggested that early behavioral changes take place during the first 2 weeks of treatment and that these changes seem to predict subsequent long-term outcome. Also, Szegedi and colleagues[19] found that early improvement using mirtazapine or paroxetine during the first 2 weeks of treatment predicted response after 6 weeks of treatment. Interestingly, Parker and colleagues[45] found a consistent reduction in depressive symptoms after 3 days of treatment with different antidepressants and a subsequent distinct course between responders and nonresponders at this timepoint. In summary, these findings support the notion that early antidepressant action is associated with a better short- and long-term outcome.

STATISTICAL ISSUES IN EVALUATING RAPID ANTIDEPRESSANT ACTIONS

In examining time course of improvement of depressive symptoms, the research design should maximize the ability to find a rapid response. For example, rating patients at too few time points could yield data that cannot assess rapid response. Leon and colleagues[29] proposed a design that might lead to proper evaluation of early improvement, suggesting that patients be evaluated twice per week. Thase[46] also suggested a more frequent application of rating scales. Similarly, Kraemer and Pruyn[47] pointed out that more frequent ratings could lead to more reliable analyses and, therefore, more powerful studies. Additionally, relatively simple measures that can be used at intervals shorter than a week could be also included in traditional trials as secondary measures to assess the speed of response to study drugs. The Life-Chart Methodology,[48] developed in the Intramural NIMH program, is an example of a rating scale that could be used at many time intervals during a study. Such ratings could be used to refine assessment of change, which is valuable in its own right, but also to help determine when more detailed rating scales should be obtained. Because of technological advances, it is feasible to perform such simple ratings at many timepoints.

Some authors have suggested that trials attempting to examine the time course for early improvement should consider the use of linear mixed models instead of repeated-measures analysis of variance.[29,49] Such models allow for the use of the most fitting variance-covariance structure for the data, which should improve the reliability of the results. Also, linear mixed models may facilitate use of cases with some missing data. Using all available data from a trial allows the use of the full sample studied instead of completers only or less reliable missing value estimates derived from the last observation carried forward.

In addition, survival analysis can be used to look at time to response or remission instead of examining response rates for various treatments.[29,46,50] Survival analysis considers the response rates in the context of the amount of time it takes to reach the specified criterion. This type of analysis provides equally valuable results with greater sensitivity to group differences given the use of timing; χ^2 approaches looking at response rates across treatment groups ignore this measure. However, reporting the proportion of patients who achieve a rapid response or remission could help clinicians evaluate the potential for achieving early response with traditional and novel therapies. Identifying subgroups of patients more likely to respond early could facilitate proper

examination of promising new drugs that may yield rapid antidepressant efficacy. Further, identification of these groups could lead to more flexible designs if dropout and adherence issues are handled appropriately for early and later responders.[51]

Finally, evaluating how early changes are related to long-term outcome will provide valuable information for determining when and how to use treatments. For instance, if early response does not predict later outcome, it may suggest that some important treatments might eventually need to be supplemented.

POSSIBLE NEUROBIOLOGICAL BASIS INVOLVED IN ONSET OF ANTIDEPRESSANT ACTIONS

The biological aspects of the first weeks of antidepressant treatment are still poorly understood. In the last decades, the monoaminergic hypothesis of depression has been considered a useful neurobiological model for explaining the delayed onset of antidepressant response. This hypothesis posits that a reliable and sustained antidepressant response can only occur after a minimum 2-week period of treatment with standard antidepressants.[32,33] Supporting this theory, Hyman and Nestler[52] suggested that a correction of disturbances in the monoaminergic metabolism is critical to achieving antidepressant response. They proposed 2 periods: an initiation period before the onset of true antidepressant effects, followed by an "adaptation phase," in which enduring modulatory changes in critical circuits related to long-term antidepressant response are present. Although study of monoaminergic systems has given us some insights into the lag of onset of antidepressant action, the resulting studies and drugs used (e.g., pindolol, stimulants) have not consistently yielded treatments that work more rapidly than existing ones. It is likely that, although important in the overall mechanism of antidepressant action, these systems are considerably further upstream of ultimately more important targets. As we have noted, most standard antidepressants exert their initial effects by increasing intrasynaptic levels of serotonin and/or norepinephrine, but clinical antidepressant efficacy is observed only after chronic administration (over days to weeks). This suggests that a cascade of downstream events is ultimately responsible for their therapeutic effects. These observations have led to the idea that while dysfunction within the monoaminergic neurotransmitter systems is likely to play an important role in mediating some facets of the pathophysiology of mood disorders, it most likely represents the downstream effects of other, more primary abnormalities in signaling pathways, in special activation of plasticity pathways.

A growing body of data supports the contention that mood disorders arise from abnormalities in cellular plasticity cascades, leading to aberrant information processing in synapses and circuits mediating affective, cognitive, motoric, and neurovegetative functions.[53–55] *Neuroplasticity* is a broad term that encapsulates changes in intracellular signaling cascades and gene regulation, modifications of synaptic number and strength, variations in neurotransmitter release, modeling of axonal and dendritic architecture, and, in some areas of the central nervous system, the generation of new neurons.[56]

Animal and human studies have shown a direct regulation of neurotrophic signaling cascades by antidepressants.[57] Research on the biological underpinnings of mood disorders has therefore begun highlighting the role of neural circuits and synapses and the plastic processes controlling their function. Information gleaned from studies of neuroplasticity in mood disorders has led to the development of new models suggesting that positive modulatory effects on diverse neuroplasticity-induced pathways are eventually associated with molecular actions that target ionic glutamatergic receptors.[54]

Several studies[58–63] have demonstrated a role for neurotrophins, cytokines, and other neurotransmitter systems in the early onset of antidepressant effects, with special focus on brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin that has been implicated in antidepressant response and that seems to increase its levels after several weeks of treatment with standard antidepressants.[58] It was demonstrated that bilateral infusion of BDNF in the hippocampus of rodents produces rapid antidepressant-like effects. Interestingly, these effects were observed less than 3 days after a single administration and persisted for 10 days.[59] BDNF and other neurotrophins may be involved in the mediation of the therapeutic effects of antidepressant treatment.

It is our contention that regulation of the neurotrophic cascades by antidepressants is perhaps more pertinent to maintenance of antidepressant response than acute response. Recent data[63,64] indicate that full antidepressant response can be achieved within a few hours, but prominent neuroplastic changes or neurogenesis would not be expected to occur in this time frame; we hypothesize that increased synaptic plasticity is involved in the acute response of antidepressants. The glutamate system appears to have a crucial role in both acute antidepressant response and maintenance of response. The study of diverse glutamatergic plasticity-enhancing agents in mood disorders, including *N*-methyl-D-aspartate (NMDA) antagonists, glutamate release–reducing agents, and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) potentiators, is leading to ever increasing insights into the mechanism of action of effective antidepressants.[60–62] For example, preliminary investigations indicate that the rapid antidepressant effect of ketamine is the result of an enhanced synaptic plasticity caused by an increased AMPA-to-NMDA glutamate receptor throughput in critical neuronal circuits.[63] This latter concept is discussed in more detail below.

Because this article focuses on studies of systems/targets that can produce antidepressant action within hours to a few days, the agents that modulate the serotonergic, noradrenergic, and dopaminergic systems will not be reviewed here. Instead, the reader is referred to some excellent reviews of this topic.[65–70]

INTERVENTIONS RESULTING IN ANTIDEPRESSANT RESPONSE IN HOURS OR A FEW DAYS

Ketamine

Accumulating evidence has revealed a common mechanism whereby dysfunction in the regulation of glutamate neurotransmission contributes to the pathophysiology of several neuropsychiatric disorders.[71–73] Glutamate receptors include AMPA, kainate, and NMDA. Supporting evidence for the role of glutamate in the pathophysiology of mood disorders and mechanism of antidepressant action comes from (1) demonstration of glutamatergic abnormalities in patients with depression, (2) glutamatergic effects of existing antidepressant and mood-stabilizing medications, (3) preclinical evidence suggesting that drugs targeting various components of glutamate neurotransmission possess antidepressant and anxiolytic properties, and (4) recent studies demonstrating the effectiveness of glutamate-modulating agents in the treatment of mood disorders (reviewed in Sanacora et al.[61]). Recently, Zarate and colleagues[64] showed that a single subanesthetic dose of the NMDA antagonist ketamine, when given intravenously, induces a rapid (within 2 hours) and sustained (1–2 weeks) antidepressant effect in patients with treatment-resistant major depression. In this study, a significant antidepressant response was found as early as 2 hours; 50% of patients met response criteria within 2 hours and 71%, by 24 hours after a single dose of ketamine. Response remained sustained for more than 1 week. This study confirmed the preliminary finding of a smaller study that also showed rapid antidepressant effects with ketamine.[74] A study underway with ketamine in patients with treatment-resistant major depression with a similar design to the 2 previous studies has found comparable response rates and time of onset of antidepressant effect (S. J. Mathew, M.D., personal communication).

To our knowledge, there has never been a report of any other pharmacologic or somatic treatment that results in such a strikingly quick and extended response with a single administration. This relatively sustained antidepressant effect may be due to early plasticity changes in critical local neuronal circuits involved in mood and behavior.[54,64,75] Ketamine has also been found to have antidepressant effects in animal models.[76,77] We hypothesize that the rapid onset of action and sustained effects seen with ketamine are the result of 2 processes. First, the resolution of core depressive symptoms within hours resulting from ketamine is not the result of neuroplastic changes, as these changes would not occur within this time frame, but is the consequence of synaptic potentiation resulting from an increase in AMPA relative to NMDA glutamatergic throughput. Second, the sustained effect of ketamine is possibly the result of early neuroplastic changes.

Regarding the acute effects of ketamine, it is well known that ketamine increases the presynaptic release of glutamate[78] and that this net increase in extracellular levels of glutamate preferentially favors AMPA receptors over NMDA as the latter type of receptors are blocked.[63] The net effect of such interplay of NMDA and AMPA receptors resulting from ketamine is an enhanced glutamatergic throughput of AMPA relative to NMDA, which leads to synaptic potentiation.[79]

To support this later contention, in animal behavioral studies, we found that in the forced swim test—a test with fairly high predictive validity in identifying antidepressant compounds—ketamine significantly decreased immobility time (a greater decrease in time spent immobile indicates "antidepressant-like properties"). In the same test, 2,3-dihydroxy-6-nitro-7-sulfoamoylbenzo[f]-quinozaline (NBQX), an AMPA/kainate antagonist, had no effects in the forced swim test when given alone; however, when NBQX was given immediately prior to ketamine and imipramine, it prevented the decrease in immobility time with ketamine but not imipramine. This finding suggests that, at least in animal models, the antidepressant-like properties of ketamine are mediated in part by AMPA receptor throughput.[63]

Taken together, these findings suggest that modulation of the glutamatergic system in the plasticity pathways, particularly linked to the cross-talk between NMDA and AMPA, may be a critical therapeutic target for obtaining rapid antidepressant actions. Ongoing studies are underway to better understand this line of research in drug development.[80]

Sleep Deprivation

Sleep deprivation has been consistently shown to induce a rapid, dramatic, and transient antidepressant effect in depressed subjects.[81] The magnitude of improvement after 1 night of sleep deprivation seems to equal the response rate for 6 weeks of antidepressant treatment.[82] Its potential advantages include its rapid short-term efficacy, that it can be tested in animals and healthy controls, and that it is both relatively safe and inexpensive. Medicated patients undergoing sleep deprivation seem to have significantly lower relapse rates compared to drug-free subjects.[81] Acute and chronic treatment with lithium has also been reported to significantly augment and sustain the rapid improvement seen during repeated, partial, or total sleep deprivation.[83–85] Different studies have also attempted to evaluate the potential efficacy of sleep deprivation augmented with strategies such as pindolol, light

therapy, and sleep synchronicity.[86–88] Recently, Benedetti et al.[89] treated 60 nonresponder patients with repeated total sleep deprivation in combination with light therapy in bipolar depression for 1 week and observed that 70% of these patients obtained response after this period. Limitations of these studies include the nonstandardization of response criteria (reaching from a 10% improvement in a Visual Analog Scale score to the standard 50% decrease in Hamilton Rating Scale for Depression [HAM-D] score). Overall, further studies using more homogeneous criteria for measuring short-term and long-term outcomes are also needed to clarify the therapeutic role of sleep deprivation for achieving rapid and sustained antidepressant efficacy.

Many hypotheses have been proposed to explain the rapid antidepressant actions of sleep deprivation[81,90] through a direct regulation in neurotransmission. Regarding the effects of sleep deprivation on plasticity pathways, changes on NMDA receptor surface expression after sleep deprivation have been found to occur,[91] which has been associated with potential rapid antidepressant actions. Furthermore, serotonin-mediated effects have been shown to decrease sensitivity of serotonergic 1A autoreceptors after total sleep deprivation.[92] Also, messenger RNA differential display, microarray, and biochemical studies[93,94] have described that, as with antidepressant treatment, sleep deprivation induces rapid up-regulation in different genes believed to be related to neuroplasticity, such as the transcription factor cAMP-Ca^{2+} response element-binding protein (CREB) and BDNF. These genes have been reported to be common final targets of existing antidepressants. Interestingly, the potential activation of plasticity-induced pathways during sleep deprivation has been shown to be predominantly mediated by the activation of noradrenergic projections in the locus ceruleus. One night of sleep deprivation has been demonstrated to stimulate hippocampal neurogenesis, but opposite effects have also been described.[95,96] It has thus been hypothesized that pharmacologic activation of the noradrenergic system during REM could generate an antidepressant effect by a mechanism similar to sleep deprivation, allowing an interaction with a sensitized postsynaptic milieu and thereby rapidly and directly increasing the expression of neuroplasticity genes.[97]

Finally, the anterior cingulate cortex (ACC) is an area that has been implicated in antidepressant response to sleep deprivation using various experimental paradigms. Positron emission tomography (PET) and single photon emission computed tomography studies show increased baseline activity in the ACC in sleep deprivation responders compared to sleep deprivation nonresponders; antidepressant response to sleep deprivation seems to be associated with a significant decrease of activation in this area.[98–100] Clark and colleagues[101,102] used perfusion-weighted functional magnetic resonance imaging (fMRI) to study the functional correlates of antidepressant response to partial sleep deprivation; they found that responders to partial sleep deprivation showed increased baseline perfusion in the left ventral ACC and in the amygdala compared to nonresponders, who had decreased perfusion following partial sleep deprivation.

Thyrotropin-Releasing Hormone

The tripeptide thyrotropin-releasing hormone (TRH) modulates serotonergic, dopaminergic, and glutamatergic transmission in cortical and limbic areas.[103–105] The potential rapid antidepressant properties of TRH have been tested over the last several decades, with mixed results.[106–108] It has been shown that intravenous administration of a single dose of TRH exerts antidepressant effects in depressed subjects within hours of treatment and that these effects persisted for 3 days.[109] Interestingly, TRH expression has been shown to be up-regulated by BDNF.[110] In contrast, negative results were ascribed to the use of a low TRH dose or to the use of an intravenous route of administration instead of an intrathecal one; the former has been reported to undergo very rapid enzymatic degradation.[111,112] To address these methodological issues, Marangell and colleagues[106] administered intrathecal TRH to 8 patients with treatment-resistant depression and measured the onset of antidepressant effect using an abbreviated version of the HAM-D. Five of 8 patients showed antidepressant response on the day of TRH administration or a day later. Interestingly, TRH was also associated with a rapid decrease in suicidality. Besides the route of TRH administration, the timing of its administration also seems to be a key issue. It has been proposed that the TRH-induced rapid antidepressant effects can be observed only if TRH is administered at night, during the circadian peak of thyrotropin receptor sensitivity.[113] For instance, nocturnal intravenous TRH was shown to induce a rapid clinical response within 24 hours of its administration in patients with bipolar depression.[108]

Further placebo-controlled studies with larger samples and the evaluation of TRH kinetics and bioavailability are necessary to confirm these promising findings with TRH and its role as a target for the development of improved fast-acting agents.

Somatic Treatments and Rapid Improvement of Depressive Symptoms

Electroconvulsive therapy. Electroconvulsive therapy (ECT) has been considered the most efficacious and rapidly acting long-term somatic treatment in psychiatry.[114] Some studies have found a faster onset of antidepressant response with ECT compared to imipramine and paroxetine.[115,116] Other studies also described significant improvement in depression after a single ECT application.[117,118] The potentially faster antidepressant response induced by ECT was shown to be correlated with a better long-term outcome.[119,120] In a cohort of 253 depressive

patients receiving ECT treatment (3 times a week), Husain et al.[121] observed that more than 50% achieved response within the first week and 83.4% responded within 2 weeks. The same group also described a sustained response in 34.8% of patients during the first week and in 64.4% within the second week (at or before the sixth ECT application). Regarding remission, 34% of patients presented remission before or at the end of week 2. Taken together, these findings suggest that ECT presents efficacy in achieving rapid improvement and response during depressive episodes in a large number of patients. Future controlled studies comparing its short-term efficacy with those of different pharmacologic and other somatic approaches may prove its utility in achieving rapid antidepressant efficacy. In addition, maintenance therapy with ECT is not commonly used, and, thus, few data show the association between early improvement and improved long-term outcome.

Other somatic interventions. Two recent studies suggested a role for repetitive transcranial magnetic stimulation (rTMS) as an augmentation strategy to achieve fast therapeutic actions in depression, although the antidepressant efficacy and biological mechanisms of rTMS remain unclear.[122,123] Similarly, deep brain stimulation appears to reduce elevated activity in subgenual cingulate (Cg25), hence producing rapid clinical improvement in treatment-resistant depression.[124–126] Mayberg and colleagues[125] similarly observed a sustained response in 5 of 6 patients after 2 months of stimulation targeting the white matter tracts adjacent to the subgenual cingulated gyrus.

NEW TECHNOLOGIES FOR BETTER UNDERSTANDING RAPID ANTIDEPRESSANT ACTIONS: A CRITICAL ROLE FOR THE DEVELOPMENT OF IMPROVED THERAPEUTICS

Besides the potential innovative approaches in the therapeutics of depression described above, new investigational tools have been proposed to present validity for predicting rapid improvement and may reveal potential endophenotypes associated with faster antidepressant response. Given our current inability to predict who will respond faster to a specific treatment, the evaluation of characteristics observed in studies using valuable technologies such as structural and functional imaging, in physiologic studies, and in genetic studies may provide a better understanding of the neurobiological basis of rapid improvement and may allow the identification of surrogate outcomes and molecular targets for the next generation of faster-acting antidepressants.

Positron Emission Tomography and Functional Magnetic Resonance Imaging

Brain imaging techniques have been used to predict time course of improvement of depressive symptoms and outcome based on baseline and early changes in brain metabolism, cerebral blood flow, receptor binding occupancy, and functional patterns of activation during the execution of specific tasks. PET studies have shown that activity in the rostral anterior (pregenual) cingulate cortex in depressed subjects before treatment can subsequently differentiate drug responders from nonresponders. Specifically, hypermetabolism in this area was in fact found to be highly predictive of posterior drug response.[127] Using PET, Wu and colleagues[99] similarly showed that baseline metabolic hyperactivity in the dorsal anterior cingulate predicted sleep deprivation–induced rapid antidepressant response. Parsey and colleagues[128] also observed a positive association between baseline 5-HT_{1A} binding potential with long-term (1 year) outcome after a depressive episode.

Morphological and functional magnetic resonance imaging studies have also been tested as predictors of antidepressant response. Greater gray matter volume changes in anterior cingulate cortex, insula, and right temporoparietal cortex have all been associated with faster antidepressant response to selective serotonin reuptake inhibitor (SSRI).[129] Similarly, increased activation of the ACC during the face emotional task also predicted rapid improvement of depressive symptoms.[129] A recent perfusion-weighted fMRI study also showed greater baseline amygdala perfusion as a potential predictor of positive clinical response to sleep deprivation.[101] In addition, differential pretreatment brain metabolism was found in patients who responded to rTMS using 1 Hz and 20 Hz. While hypometabolism predicted positive response to 20-Hz rTMS, hypermetabolism was associated with a better outcome with 1-Hz rTMS.[130]

Electrophysiologic Tools for Measuring Synaptic Plasticity Changes

The study of early plasticity associated with neuroimaging findings as a tool for detecting rapid antidepressant action is a promising area. Indirect proof of synaptic plasticity in patients with depression has been gathered through high-density electroencephalogram (EEG) sleep and magnetoencephalography studies. Studies performed by Tononi and Cirelli[131] (University of Wisconsin) evaluating healthy subjects have shown that rTMS induces a localized potentiation of TMS-evoked cortical EEG responses, which represent a long-term potentiation in human cortex, thus replicating the classic paradigm previously studied in animals.[132,133] These changes occur together with an increase in slow-wave activity, which may be considered a marker of synaptic plasticity.[131] Another promising area is the study of baseline and early changes in slow-wave activity and their correlation with antidepressant response.

Studies with magnetoencephalography are underway to evaluate the early effects of antidepressant drugs that

putatively exert their therapeutic effects through an increase in synaptic plasticity, such as ketamine, by measuring evoked magnetic fields related to clinical outcome. Because magnetoencephalography uses source localization that allows good spatial resolution with a greater temporal resolution than fMRI, it can also be used to study baseline activity and early functional changes associated with antidepressant treatment during different cognitive tasks.

All of the brain imaging and electrophysiologic tools mentioned above can thus effectively be used to predict the outcome of currently available treatment strategies in order to elaborate treatment algorithms that could in the future guide clinical decisions of whether to switch or continue with a specific treatment. The use of neuroimaging and electrophysiologic techniques for predicting early antidepressant response is a promising area for current and future studies on rapid antidepressant response.

Actigraphy

Actigraphy is a high resolution method for measuring circadian rhythm and sleep activity characteristics in different time series; it has recently been used to evaluate diverse treatment effects regarding regulation in the rest-activity cycle.[134] For example, a miniaturized wrist-worn device with enough capacity to record longer periods with minimal influence on patients' lifestyle has been used to identify clinical subtypes of depression related to antidepressant effects, which may provide further insight regarding the pathophysiology of depression.[135] This tool might be particularly useful for predicting short- and long-term improvement associated with specific sleep patterns.

Pharmacogenetics

The goal of studying the pharmacogenetics of antidepressants is to achieve new insights regarding potential candidate genes involved in the molecular and clinical effects of several classes of antidepressants, thus providing further insights about their mechanisms of action and relevant therapeutic targets associated with prediction of faster antidepressant response. For instance, studies have found that enzymes of the cytochrome P450 (*CYP*) family of genes are directly involved in diverse regulatory effects of the monoaminergic system, and polymorphisms in the *CYP2D6* and 5-HT transporter promoter (*HTTLPR*) have been widely associated with pharmacokinetics and clinical response to diverse antidepressants.[136]

CYP2D6 polymorphisms have been found to influence dose-response and serum levels of antidepressants, and may be a useful tool for agents presenting dose-response windows, such as some of the tricyclic antidepressants.[137] Many studies have evaluated the role of polymorphisms of *HTTLPR* in the antidepressant response of different SSRIs in Caucasians.[138–140] In these studies, clinical response was associated with a long variant (L-allele) of the *HTTLPR*. Durham and colleagues[139] observed that depressed elderly subjects with this polymorphism had a faster onset of response to sertraline; however, there was no association between clinical effect and this polymorphism for agents other than SSRIs.[140,141] Serretti and colleagues,[142] in a meta-analysis including 15 studies and 1435 subjects, observed a significant association between the *s/s* variant of the *5-HTTLPR* and antidepressant response to SSRIs and sleep deprivation. A significant association was also found between treatment response and remission and the *HTR2A* gene (which encodes the 5-HT_{2A} receptor) in a large sample (N = 1380) of depressive subjects treated with citalopram.[4] Recently, Tadic et al.[143] found an association between the MAOB A644G intron 13 single-nucleotide polymorphism (SNP) and antidepressant response in females.

Functional polymorphisms of genes involved in hypothalamic-pituitary-adrenal (HPA) axis regulation, especially glucocorticoid receptor (GR) sensitivity, have been shown to confer susceptibility for developing depression and antidepressant response. A 3-SNP haplotype into the corticotropin-releasing hormone receptor 1 (*CRHR1*) was associated with antidepressant response to fluoxetine or desipramine.[144] In addition, faster antidepressant response and improved cognitive function were linked to polymorphisms on the GR gene (codons 22 and 23-ER22/23EK), which is responsible for increasing GR resistance.[145] The same group also found an association between a SNP on GR sensitivity–regulating chaperone *FKBP5* and rapid response to antidepressants, possibly related to the restoration of HPA axis physiologic function.[146,147] Interestingly, these polymorphisms on *FKBP5* are associated with its overexpression, leading to GR insensitivity and elevated plasma cortisol levels.[136]

Taken together, these promising pharmacogenetic findings support a central role for genes regulating these systems in rapid response and improved outcome in depression. The greater our understanding of such individual differences, the more likely clinicians will be to identify subgroups of depressive subjects who will respond better to specific treatments, thus limiting the risks associated with lack of efficacy and treatment resistance.

APPROACHES FOR ACHIEVING RAPID ONSET OF ANTIDEPRESSANT ACTION: WHERE DO WE GO FROM HERE?

As the evidence reviewed in this article emphasizes, it is crucial to redefine the way we understand and define the clinically relevant concepts associated with the therapeutics of depression. The model currently used has focused on weekly evaluation of available pharmacologic approaches; such evaluations yield mainly small

differences between agents that are known to have limited potential to induce rapid antidepressant actions.

A faster and sustained antidepressant response represents a key challenge in the development of new effective therapeutics for depression and may prevent the deleterious neurobiological and psychosocial effects secondary to recurrent or unremitting depressive episodes. Rapid onset of antidepressant action occurring within hours or days instead of weeks or months can and should be our overall goal. This new paradigm in the therapeutics of depression is expected to include not only the development of novel and improved therapeutics, but also the development of tools that enable us to evaluate antidepressant efficacy within hours or days of first administration; many other areas of medicine such as cardiology, neurology, oncology, and endocrinology currently have the tools necessary to evaluate therapeutic onset quickly and reliably. Furthermore, as our understanding of the genetics of depression expands, this knowledge can be used to inform decisions about which patients are likely to respond to which therapeutic approach. A combination of these 3 facets—better therapies, better evaluative tools, and better understanding of a patient's genetic profile—has the power to revolutionize current conceptions and treatments for depression.

Regarding the development of novel therapeutics, it should be pointed out that many substances are capable of inducing transitory euphoria and hyperactivity (also including psychomimetic effects) limited to the half-life of the compound being administered, but these effects cannot be characterized as a true improvement of core depressive symptoms. Thus, rapid and sustained antidepressant effects (in core depressive symptoms and constructs) well beyond the half-life of the drug being administered may be considered a key hallmark of new pharmacologic treatments potentially able to produce rapid antidepressant actions.

New interventions able to induce rapid antidepressant actions may rapidly restore disrupted neuronal circuitry, thus improving symptoms, functional well-being, and quality of life. Thus, the discovery of novel antidepressants that achieve antidepressant response and remission in a shorter period of time should be a priority in mood disorder research. Clinical and preclinical studies have been performed in this area, searching for genes, signaling pathways, and/or neurochemical circuits that might be involved in these therapeutic effects. Potential targets for future studies in this area include common targets related to (1) glutamatergic modulation; (2) neuro-biomolecular basis for sleep, wakefulness, and sleep deprivation; and (3) modulation of limbic-cortical circuits (e.g., stimulation of subgenual cingulate white matter with deep brain stimulation).

In terms of instruments that measure early improvement, present evaluative strategies fall short. For instance, if ratings are only obtained weekly, then early response and identification of key symptoms/clusters predictive of ultimate response—perhaps occurring within hours or days of administration—will be missed. In this context, future study designs evaluating rapid improvement may require a duration of only 2 weeks, which would have the advantage of exposing fewer patients to an experimental compound. Such pilot studies would then inform the design of future ones. These studies will also need to have both a placebo and an active comparator arm.

We propose that research on rapid antidepressant actions should occur on 2 fronts. The first front is to identify specific symptoms or clusters that respond quickly to current antidepressant treatments and that predict sustained improvement either for all patients or for a subset of patients. Defining such characteristics would help personalize treatment, so that early changes (or conversely, the absence of early changes) could help physicians determine whether patients should remain in a particular trial. Patients could thus avoid trials that are not likely to result in improvement.

The second major focus should be in designing antidepressants that work rapidly—within hours or a few days. There is abundant evidence from other areas of medicine that this goal is possible. For example, high blood pressure or blood glucose, pain, or a migraine attack can all be averted within a few hours. In other words, our current expectations regarding antidepressant treatments are too low; instead of assuming that patients will respond within weeks or months, we should expect and be able to measure properly antidepressant treatments that might work within hours or days. Fortunately, much of the ongoing research into antidepressant strategies holds considerable promise. It is our hope that such research will raise the bar for developing the next generation of faster-acting and more effective antidepressants to better treat this devastating illness.

Drug names: desipramine (Norpramin and others), citalopram (Celexa and others), diltiazem (Cartia, Taztia, and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), ketamine (Ketalar and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), pindolol (Visken and others), sertraline (Zoloft and others), sumatriptan (Imitrex), verapamil (Verelan, Covera, and others).

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