
Developing Novel Treatments for Mood Disorders: Accelerating Discovery

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This review was generated from discussions by the Pharmacologic and Somatic Treatments Section of the National Institute of Mental Health Strategic Plan for Mood Disorders Committee on advancing novel pharmacologic and somatic treatments for mood disorders. The opening section of the article summarizes in broad strokes, current pharmacologic treatments, and new directions in the field. Thereafter the topics focus on specific research initiatives that could advance the current therapeutics for mood disorders including new basic and clinical research in vivo human imaging procedures, somatic therapeutics, and the vast new area of pharmacogenetics. New scientific and technical opportunities exist today based on advances in basic neuroscience, opportunities in clinical testing, industry interest in advancing central nervous system therapeutics, and on active consumer advocacy groups. The question of how to bring all of these positive forces together to accelerate discovery in mood disorder therapeutics is the topic of this article.

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Introduction

Depression is one of the most pervasive and costly brain diseases. It affects more than 20 million Americans, significantly more women than men; it shows an overall lifetime prevalence rate in the United States of 17.1% and comparable figures worldwide. It not only accounts for much pain and suffering but also significant days of lost work; it is associated with several comorbid psychiatric disorders and often goes undetected, especially in children and adolescents. The illness has 10% mortality due to suicide and a presumption of increased rates of serious accidents among persons with active mood disorders. It is a major risk factor for the development of coronary artery disease and stroke and possibly other major medical disorders. Although neither the neurobiological mechanisms of mood-related illnesses nor even an understanding of normal mood regulation are known, elucidation of the biological contributors to normal and pathologic mood is progressively accumulating. Such constituents of mood include not only the putatively involved neurotransmitter systems of serotonin, norepinephrine, dopamine, and acetylcholine, but also the influence of two endocrine axes, the hypothalamic-pituitary-adrenal (HPA) and hypothalamic pituitary-thyroid (HPT) axes, as well as alterations in immune function. Treatments exist, but response to medication is not inevitable, is frequently incomplete, and is often accompanied by limiting side effects. The two major classes of antidepressants developed have been the tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs).

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Monoamine oxidase inhibitors (MAOI) also have played a theoretical and practical role in therapeutics. A rich pharmacopeia for the treatment of depression has been developed in only 40 years; however, it is startling that, with the exception of modifications to the existing monoamine-based strategies, the last true innovation in the area of antidepressant treatment occurred decades ago.

Advances in basic neuroscience have provided a rich and increasingly mature knowledge base for understanding pathophysiology and developing rational pharmacotherapy in brain diseases. New discoveries based on novel experimental techniques have repeatedly provided human brain research with emerging models of neural mechanisms that will potentially contribute to disease understanding, as well as a more comprehensive understanding of current drug action. Progress in the Human Genome Project has actually been faster than predicted and will contribute exponentially to identification of pathology in mood disorders. Brain regions involved in the modulation of mood are being delineated with considerable precision and cross-laboratory consistency. Several neurotransmitter systems and their metabolic pathways have been elucidated, including glutamate, γ -aminobutyric acid (GABA), serotonin, norepinephrine, and dopamine, as have the membrane-bound signal transduction elements and the intracellular signaling systems, which modulate gene transcription and protein synthesis. Clues to mechanisms for novel selective pharmacologic manipulation are increasingly evident. Studies of the mechanisms of action of effective antidepressant drugs are converging around speculations of a common set of intracellular actions. This concatenation of new knowledge will progressively contribute to new therapeutics and allow scientists interested in mood disorders to think differently about drug targets.

The major question addressed in this article is how to accelerate the process of discovery in mood disorder treatments so as to make quantum leaps toward novel treatment techniques. What needs to be done, and where can the elements of discovery be carried out most efficiently? What roles should government, patient advocacy groups, academia, and industry play? A rational plan that is compelling enough to engender widespread support from all stakeholders, cooperation among scientists, and interest from funding sources would be ideal. Even focused funding initiatives in a critical area can shape the direction of the field. If cooperation is maximized, new discoveries and treatments will result.

Fortunately, the National Institute of Mental Health (NIMH) is able to take advantage of the experience of other groups within the National Institutes of Health that have posed similar questions of how to develop novel and better therapeutics. For example, the National Cancer Institute (NCI) has had a drug development program for

anticancer drugs for more than 20 years that was started in an era when pharmaceutical companies were not aggressively pursuing treatments for cancer. The NCI has recently articulated the goal of encouraging mechanistically novel drug development for cancer treatments. It currently supports a complex set of modular mechanisms, including repositories of drugs, natural products, research tools, and information, as well as preclinical and clinical drug development services all available to NCI grantees and small business contractors (<http://dtp.nci.nih.gov>). The National Institute of Allergy and Infectious Diseases (NIAID) has developed a program for drug development in AIDS to facilitate new therapies and, when necessary, support preclinical and clinical development. NIAID also has a modular, flexible but integrated preclinical/clinical grant program for academia and a contract program for small business researchers to facilitate drug development not only for AIDS but also for its accompanying opportunistic infections; they aim to target research to gaps in treatment knowledge (http://www.niaid.nih.gov/aids_therapeutics). In the process of these efforts, NCI in cancer therapeutics and NIAID in target infectious diseases, have both developed a clinical trials networks with well-trained clinical scientists who not only conduct scientific trials, but also develop improved rating scales for specified clinical end points and focus on identifying biomarkers for drug action. These institutes use grant and contract mechanisms for these programs, they collaborate on research and development projects of mutual interest with for-profit companies, and they have publicly accessible databases of compounds and substantial compound repositories for public use. The National Institute on Aging (NIA) also has a drug development program in Alzheimer's disease (AD) that is predominantly grant based with respect to its research but also includes a clinical trials network. This group of clinical investigators works together to test new drug strategies for AD and, in parallel, develops new diagnostic and dimensional rating scales; it also seeks biomarkers to identify successful treatment response. These potential models, already active in other branches of the NIH, have as their goal to encourage and facilitate innovative drug development based on rational pathophysiology. They include successful clinical trial networks, and some have suggested that these are one of the most critical contributions of NIH institutes in attaining the goal of new treatment development.

Current Status of Drug Treatments for Mood Disorders and Directions for the Future

Medications for the treatment of depression and bipolar disease were introduced in the late 1950s and early 1960s

as part of what is commonly referred to as the *psychopharmacology revolution*. Two classes of antidepressant medications were originally identified, TCAs and MAOIs. A second major wave of new antidepressants occurred in 1988 when the first SSRI, fluoxetine, was introduced. More recently venlafaxine, nefazodone, and mirtazapine have been introduced in the United States and reboxetine, milnacipran, moclobamide, and tianeptine in Europe, Asia, or Canada.

Antidepressant Medications Currently Used for the Treatment of Depression

OLDER LINE AGENTS: TCAs AND MAOIs. The TCAs were the first line medication therapy for depression for nearly 30 years, until the introduction of the SSRIs. These medications can be further divided into two main classes (Potter et al 1998). The tertiary amines (e.g., amitriptyline and imipramine) are drugs that are generally dual (i.e., serotonin [5HT] and norepinephrine [NE]) reuptake inhibitors, are metabolized to secondary amines, and have a high burden of anticholinergic side effects. The secondary amines (e.g., nortriptyline and desipramine) are generally more selective at blocking NE reuptake with somewhat reduced anticholinergic side effects. The TCAs have well-documented efficacy in the treatment of major depression, with some still equivocal evidence that the tertiary amines are more effective than secondary amines for severe depression (Anderson 2000). These agents are lethal in overdose, however; in fact, they remain the number one cause of overdose death among prescription drugs in the United States and worldwide. They also produce a range of potentially serious side effects, some of which involve the cardiovascular system.

Three MAOIs are now available in the United States, phenelzine, tranylcypromine, and isocarboxazide. These are irreversible MAOIs that inhibit the enzymatic degradation of both MAO-A and MAO-B. They are best used by titrating dose to approximately $\geq 80\%$ inhibition of MAO-B. Strict dietary restrictions must be observed when taking MAOIs because there are potentially life-threatening drug–food interactions. There is evidence that MAOIs are more effective than TCAs (and perhaps SSRIs) for atypical depression (characterized by hypersomnia, hyperphagia, reverse diurnal mood variation, and prominent fatigue), as well as in persons who do not respond to other antidepressants (McGrath et al 1993; Stewart et al 1997); however, because of the adverse side effect profile, they are at present generally reserved for patients who are refractory to other medications.

FREQUENTLY USED DRUGS. The SSRIs are clearly the drug treatment of choice for all forms of depression in the United States. Five are now available: fluoxetine, sertraline, paroxetine, fluvoxamine (which is not approved for

depression by the Food and Drug Administration [FDA]), and citalopram (Charney et al 1998). These drugs are approximately equivalent to each other and to TCAs in efficacy, although some evidence suggests that the tertiary amines may be more effective than SSRIs for severe depression (Anderson 2000). The SSRIs have a much more benign side effect profile than TCAs and, largely for this reason, have replaced TCAs as first line therapy. The SSRIs are structurally distinct and, although they share the common property of 5HT reuptake blockade, each produces additional effects that render them different from each other (Owens et al 2000). Indeed, paroxetine is a dual 5HT/NE reuptake inhibitor, and sertraline is a dual 5HT/dopamine reuptake inhibitor (Tatsumi et al 1997). A major problem of the SSRIs (and indeed of all drugs that block the reuptake of serotonin) is sexual dysfunction (Rosen et al 1999). A serotonin reuptake inhibitor that shared the good efficacy and side effect profile of available SSRIs but lacked the propensity to cause sexual dysfunction would represent a significant therapeutic advance.

There are several other effective antidepressants that have been introduced since the TCAs that are frequently used but do not fall conveniently into any single categorization. Trazodone is a weak serotonin reuptake inhibitor and a potent 5HT₂ receptor antagonist, which possesses antidepressant activity at high doses but is usually used as a hypnotic (Haria et al 1994). Nefazodone is a potent 5HT₂ antagonist and also a NE and 5HT receptor inhibitor (Owens et al 1995). Venlafaxine is a dual (serotonin and norepinephrine) reuptake inhibitor but is not a tricyclic drug (Andrews et al 1996). Mirtazapine is a α_2 -receptor antagonist that increases presynaptic release of both serotonin and norepinephrine (de Boer 1996) and is also a 5HT₂ and 5HT₃ antagonist. Because of advantages in the side effect profile and possibly in efficacy, these drugs are often used as first-line agents.

MEDICATIONS USED FOR THE TREATMENT OF BIPOLAR DISORDER. The treatment of depression in patients with bipolar disorder remains inadequately researched and consequently a source of confusion for clinicians. It is generally agreed that all bipolar patients should be maintained on a mood stabilizer. Of these, the most commonly prescribed are lithium and the anticonvulsant valproate. When patients with bipolar illness become depressed, the first step is to initiate mood stabilizer therapy. If the patient is already on a mood stabilizer at the time of depression onset, there are data to suggest that maximizing the dose may effectively treat the depression (Nemeroff, in press); however, when this fails, it is often necessary to add an antidepressant. The risk of placing a bipolar patient on an antidepressant is the induction of a switch in mood to hypomania or mania or the induction of rapid cycling, but estimates on how commonly these occur vary (Alt-

shuler et al 1995). Some data suggest that TCAs are more likely than MAOIs or SSRIs to cause mania in bipolar patients (Kalin 1996). It is commonly believed that the antidepressant bupropion is the least likely of all antidepressants to produce manic shift, although the database supporting this contention is meager (Sachs et al 1994). Recently, it has been shown that the anticonvulsant lamotrigine, which acts in part by modulating glutamatergic neurotransmission, may be particularly effective in treating depression in the bipolar patient without inducing mania (Calabrese et al 1999). Major research tasks are to determine whether these differences in propensity to induce manic shifts are real and then to define unique aspects of the mechanism of action of agents that are less likely to cause manic shift but are still effective in treating bipolar depression.

MEDICATIONS USED FOR TREATMENT REFRACTORY PATIENTS. About 30% of patients with depression do not respond (i.e., exhibit a 50% or greater reduction in symptom severity) to an initial course of a single antidepressant agent (Fava and Davidson 1996). A higher percentage, perhaps 70%, is not brought into complete remission by antidepressant monotherapy. Some of these nonresponders, after the monotherapy is maximized, are switched to another antidepressant, usually from another class. Another approach is to attempt to “potentiate” the effect of the prescribed antidepressant by adding another agent that is not itself an antidepressant. There is a long-list of such adjuncts, but among them are psychostimulants and dopamine agonists (e.g., methylphenidate, amphetamine, modafenil, pramipexole), anticonvulsants (e.g., valproate, lamotrigine, gabapentin, topiramate), lithium, triiodothyronine (T_3), gonadal steroids (e.g., estrogen, testosterone), or atypical antipsychotics (Nemeroff 1996). The best-controlled data for efficacy as augmenting agents is for T_3 and for lithium, although the recent atypical antipsychotic data are impressive.

DRUGS USED TO SPEED THE ONSET OF ACTION OF ANTIDEPRESSANTS. Most patients with depression do not exhibit a therapeutic response until they have taken the drug for at least 3 to 5 weeks. A number of agents have been used as add-ons to established antidepressants in an attempt to reduce this latency to response. So far, systematic evidence that any such agent is effective in this regard is lacking. There are some data, however, that the addition of benzodiazepines (Smith et al 1998), 5HT_{1A} antagonists (e.g., pindolol; Blier and Bergeron 1998), or α_2 -antagonists (e.g., yohimbine; Cappiello et al 1995) may speed the onset of antidepressant action.

HERBAL REMEDIES. “Off the shelf” herbal remedies are self-prescribed by many individuals for the relief of depression, but they are not regulated by the FDA (Ernst

et al 1998). Therefore, there is virtually no information on efficacy, adverse events, or drug–drug interactions of these agents, nor is there any regulation of drug composition. Moreover, in most cases the possible mechanism(s) of action of these compounds is obscure. Nevertheless, some studies, however flawed, have suggested that substances such as St. John’s Wort (hypericum) or S-adenosyl methionine may have antidepressant properties; however, recently, two controlled studies failed to demonstrate that St. John’s Wort is more effective than placebo in the treatment of depression (Davidson et al, in press; Shelton et al 2001).

Medications Currently under Development

SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS. Although medications that are believed to act primarily as selective NE reuptake inhibitors are effective in treating depression, the only ones available in the United States are heterocyclics. One selective NE reuptake inhibitor, reboxetine, is available in several European countries and Canada but has not been approved in the United States. As expected, it has a more distinct adverse side effect profile than the SSRIs (Kasper et al 2000), with urinary and cardiovascular side effects of greatest concern.

DUAL REUPTAKE INHIBITORS. There is some evidence, although it is not universally accepted, that dual reuptake inhibitors work more quickly or are more efficacious than single monoamine reuptake inhibitors (Anderson 2000; Thase et al 2001), although at least one study did not confirm these findings. Available dual reuptake inhibitors include the tertiary TCAs and venlafaxine. Other dual reuptake blockers, such as duloxetine, and milnacipran, are under development in the United States, although the latter is available in several countries including Japan and France (Sharma et al 2000).

DRUGS THAT INVOLVE DIRECT OR INDIRECT DOPAMINE RECEPTOR AGONISM. There is some limited evidence that drugs that enhance dopaminergic neurotransmission may have antidepressant properties. This is not surprising in view of the fact that there is growing evidence for a reduction in the activity of certain dopamine (DA)-containing circuits in depressed patients. Thus, pramipexole, a DA receptor agonist, has been reported to be as effective as fluoxetine in treating depression. A previously available medication, nomifensine, which is a potent DA reuptake inhibitor and an effective antidepressant, was withdrawn from the market because of adverse events (rare hemolytic anemia). Therefore, novel DA reuptake inhibitors, including some that are also 5HT or NE reuptake inhibitors, are currently under development. As noted earlier, sertraline is the only SSRI with potent DA reuptake antagonist properties.

DRUGS THAT COMBINE SEROTONIN REUPTAKE INHIBITION WITH 5HT₂/5HT₃ ANTAGONISM. Several currently available antidepressants are antagonists of postsynaptic serotonin receptors. This is thought to change the adverse side effect profile that is associated with enhancing serotonin neurotransmission. For example, nefazodone clearly has reduced sexual side effects compared with SSRIs, and this may be due to its potent 5HT_{2A} antagonism (Ferguson et al 2001); mirtazapine shares this absence of sexual dysfunction as well as reduced incidence of nausea mostly due to 5HT_{2A} and 5HT₃ receptor antagonism (Gelenberg et al 2000). Antianxiety and hypnotic effects have also been associated with antagonism of the 5HT₂ receptor. Nevertheless, evidence proving that there is a link between postsynaptic receptor effects and these adverse events remains incomplete. Nevertheless, drugs that combine serotonin reuptake antagonism with 5HT₂ and/or 5HT₃ antagonism are being developed.

CORTICOTROPIN-RELEASING FACTOR (CRF) RECEPTOR ANTAGONISTS. Abundant evidence suggests that increased production and/or release of CRF within the central nervous system (CNS) occurs in patients with posttraumatic stress disorder (PTSD) and major depression (Heim and Nemeroff 1999). Preclinical studies have revealed that CRF receptor antagonists have anxiolytic and antidepressant properties. Hence, there is a solid rationale to support CRF receptor antagonists as a novel class of antidepressants and anxiolytics. At least one CRF antagonist has been studied in an open-label design, suggesting antidepressant efficacy (Zobel et al 2000); however, a multisite placebo-controlled, double-blind, randomized clinical trial with a CRF receptor antagonist has yet to be completed for the outcome of this strategy to be evaluated.

Two compounds that act as antagonists for the low affinity glucocorticoid receptor (GR) are currently being studied in patients with severe major depression without psychotic features (ORG 34517) or with psychotic features (mifepristone or C-1073). A recent preliminary report indicates that mifepristone can produce a very rapid reduction in psychotic symptoms in patients with major depression (Belanoff et al 2001) in keeping with the earlier hypothesis that excessive HPA axis activity plays a key role in the development of cognitive impairment or psychosis in depressed patients (Schatzberg et al 1985).

SUBSTANCE P (NEUROKININ) RECEPTOR ANTAGONISTS. Based on preclinical evidence suggesting anxiolytic properties of inhibitors of the Substance P receptor, also known as the neurokinin I (NK₁) receptor, selective compounds have been tested. Several NK₁ antagonists have been tested in rigorous designs, and in one study Substance P was found to be superior to placebo and equal

to active comparators in treating depression (Kramer et al 1998; Stout et al 2001). There are a number of ongoing trials of novel NK₁ antagonists in a variety of disorders ranging from depression to generalized anxiety disorder and panic disorder. Indeed, several candidate NK₁ receptor antagonists, and some antagonists of other NK receptors, are currently under development for the treatment of depression.

DRUGS THAT MODULATE GLUTAMATERGIC NEUROTRANSMISSION. The excitatory amino acid glutamate has been linked to a variety of psychiatric disorders, including anxiety and depression, and in inhibition of neurogenesis or contribution to neurodegeneration. Glutamate neurotransmission involves several distinct types of receptor, generally categorized as ionic or metabotropic. Antagonists of postsynaptic glutamate receptors (e.g., NMDA antagonists) and medications that reduce presynaptic release of glutamate (e.g., mGluR agonists) are among the candidate medications under development as potential antidepressants (Mathew et al, in press).

Targets for Future Antidepressant Research

DRUGS THAT INTERACT WITH SECOND MESSENGER SYSTEMS. After binding to postsynaptic receptors, monoamines and other neurotransmitters initiate a cascade of intraneuronal events that include effects on a variety of second messenger systems including cAMP and PIP (Hyman and Nestler 1996). Evidence suggests that, in general, activation of certain of these pathways is necessary for the action of currently available antidepressants. Consequently, medications that act directly on second messenger systems, such as rolipram, may be effective antidepressants.

DRUGS THAT INTERACT WITH RESPONSE ELEMENTS AND TRANSCRIPTION FACTORS. There is also evidence that antidepressants stimulate the expression of early immediate genes, phosphorylation of protein kinases, activity of response elements such as cAMP response element binding protein, and the activity of transcription factors (Duman et al 1997). Each of these elements is a potential target for antidepressant drug development. For example, there is reason to believe that phosphorylation inhibitors active in the CNS may possess antidepressant activity.

DRUGS THAT ENHANCE NEUROPROTECTIVE AND NEUROGENIC FACTORS. In recent years, it has been unequivocally demonstrated that, in contrast to previous notions, neurogenesis occurs in the adult brain particularly in the dentate gyrus of the hippocampus. Moreover, there is evidence that depression and stress may interfere with neurogenesis, perhaps in part by inhibiting the activity of neurogenic factors such as brain-derived neurotrophic

factor (BDNF) or of antiapoptotic genes such as *bcl2*. Thus far, all somatic treatments known to be effective in treating depression, including electroconvulsive therapy (ECT), have in common the property of stimulating the expression of BDNF (Duman et al 1997), and those tested also enhance neurogenesis (Duman et al 1997). At least one validated animal model of depression, maternal deprivation, is associated with reduced hippocampal neurogenesis (Plotsky et al, unpublished data). Hence, molecules that enhance neurogenesis, including neurogenic and neuroprotective factors, could function as antidepressants.

DRUGS THAT MANIPULATE CYTOKINE RECEPTORS AND ACTIVITY. There is limited and controversial evidence that changes in the expression of cytokines and other molecules usually associated with immune function may be involved in the pathogenesis of depression. Cytokines are expressed in the brain, and during development they play important roles in normal brain embryogenesis. A recent study revealed that induction of increased cytokine activity was associated with depressed mood in normal volunteers (Duman et al 1997). Elevated IL-6 concentrations in plasma have been reported in depressed patients (Musselman et al 2001). Should further work confirm a relationship between cytokines and depression, medications directed at cytokines might represent novel antidepressants.

DRUGS THAT MODULATE NEUROTRANSMITTER TRANSPORTER TRAFFICKING. Because drugs that inhibit 5HT and NE transporters are mainstays in our current arsenal of antidepressant medications, it is reasonable to consider that drugs that alter the surface expression of these proteins might possess clinical utility. Recent studies have revealed that the 5HT and NE transporters are regulated by intracellular kinase and phosphatase-dependent trafficking pathways that ultimately alter the density of transporters on cell membranes (Bauman et al 2000; Blakely et al 1998; Ramamoorthy and Blakely 1999). Whether current antidepressants influence the trafficking of transporter proteins *in vivo* remains unknown. Nevertheless, as the signal transduction pathways underlying phosphorylation-based changes in transporter surface expression are unraveled, new targets for pharmacologic intervention may be uncovered.

How Does Mood Disorder Research Advance Novel Treatments?

The pathophysiology underlying mood disorders remains obscure. Consequently, there are few primary biological targets toward which to direct new therapeutics development. Current treatments for mood disorders have been largely developed based on serendipitous clinical observa-

tion. These were critical observations—not of mechanism, but of clinical response. The ability first of clinical and then of pharmaceutical scientists to move basic and clinical observations into effective clinical treatments represent advances that, in their time, made a difference in many lives and cannot be overlooked. Furthermore, these observations provided clues for mechanistically oriented basic scientists to develop even newer treatments. Nevertheless, it is now time to forge ahead with new clinical research based on the numerable advances in neuroscience.

Scientists agree that finding the critical pathophysiologies in mood disorders will facilitate movement toward treatment, leading more quickly than any other pathway to novel therapeutic candidates. This rapid movement, based on known pathophysiology, has taken place in almost every medical discipline and is perhaps best exemplified in recent years in Alzheimer's disease research. Clearly, the first answer to the question of how to move novel drug discovery ahead is to facilitate basic discovery. This is not as simple as merely increasing basic research support; in addition, funding mechanisms must be specifically targeted so as to direct relevant basic ideas and projects toward application in the areas of disease pathophysiology and drug target development. Indeed, the NIMH and other mental health funding entities already support these directions. Within NIMH, movement toward consolidating disparate programs each having a goal of novel treatment development, would facilitate this process. The common problems of rigidity in pharmacologic ideas and clinical concepts, both for investigators and grant reviewers, failure to incorporate the newest technologies into applied approaches, and utilizing the same old research methodologies, still serve as obstacles to new drug discovery in the R-O1 grant mechanism for basic research. Innovative thinking in basic research and incentivizing its applied aspects from the best laboratories could advance innovations through federally funded initiatives.

Many of our best treatments for mood disorders have been used as pharmacologic models for further discovery. Although there have been few other options in therapeutics research to date, this strategy has had both advantages and disadvantages. On the one hand, it has provided new treatments with marginally improved therapeutic action, but considerably improved side effect profiles. On the other hand, when used as a direct template without the benefit of new basic research, it has not provided the field with substantially innovative treatments. In contrast, when creative basic scientists directly study common antidepressant or antimanic drug action at cellular and molecular level, new observations have emerged which may underlie new therapeutic directions. For example, the actions of lithium and other mood stabilizers on intracellular signaling cascades may redirect treatment targets in these areas.

One of the critical elements of successful drug discovery is the involvement of astute, well-trained clinicians in designing clinical methodologies, defining outcome criteria in validated disease entities, and developing suitable surrogate measures that track drug response. Such a program requires a network of sites and scientists. The days of the isolated clinical experimentalist making critical contributions are largely past. Networks of trained, observant clinicians with “real-world” patient volunteers, representative of actual treatment populations, are needed to service the promise of basic discovery. Problems with clinical trials in psychiatry, particularly in mood and anxiety disorder, are so severe that industry enthusiasm for drug discovery waxes and wanes with virtually each clinical trial. All clinical investigators in industry and academia alike are painfully aware of these problems: high placebo response rates that compromise the identification of drug–placebo differences; clinical trials that garner dropout rates higher than 50%; poor patient volunteer screening criteria allowing patients with poor or compromised response rates into the test populations; and the lack of outcomes other than clinical response, namely, the absence of one or more critical neurophysiologic responses corresponding to the drug’s therapeutic action. In other NIH branches, successful programs responsible for bringing new treatments to development, do so with experienced, well-developed clinical networks, and new clinical methodologies are created in the process.

An additional benefit of such a multisite clinical network is to provide the practitioners pool with knowledge and techniques garnered from research, which are then extended into clinical practice. Such a cadre of scientists will infiltrate not only clinical practice but industry to improve clinical testing there, and into governmental offices (FDA, NIH, CDC) to affect applied research endeavors.

What Is the NIMH Already Doing to Facilitate Drug Development?

BASIC RESEARCH FUNDING. The NIMH funds basic neuroscience research pertinent to depression and mania mechanisms, particularly the R-O1 grants. Much of this work focuses on disease target identification. Currently, the NIMH provides support for the identification of novel targets through the Brain Molecular Anatomy Project (BMAP). The goal of BMAP is the discovery of novel genes expressed in the developing mouse nervous system and the development of resources for the neuroscience community. The genetic resources made available through BMAP include: the identification of 3′- and 5′-expressed sequence tags (ESTs) from adult mouse brain; the generation of cDNA libraries from 10 brain regions (hippocampus, striatum, basal ganglia, amygdala, frontal cortex,

hypothalamus, pineal gland, olfactory bulb, brain stem, cerebellum), the spinal cord, and the retina in the adult mouse using strain C57BL/6/J; and a nonredundant arrayed set of more than 20,000 mouse brain cDNA clones (<http://www.resgen.com/products/BMAP.php3>). In addition, because the primary targets of many clinically important medications are membrane receptors, new initiatives in the Intramural Research Program at NIMH include the isolation, cloning, and characterization of novel human G-protein coupled receptors and orphan receptors (<http://intramural.nimh.nih.gov/research/log/>).

NOVEL COMPOUND SCREENING. The NIMH Psychoactive Drug Screening Program (PDSP) was instituted to aid investigators in the design and development of new chemical entities and small molecules to be used as research tools, probes, drug delivery vehicles, potential therapeutic agents, and positron emission spectrometry (PET) or single photon emission tomography (SPECT) ligands for brain imaging. New chemical entities and natural products can be screened for pharmacologic and functional activity at a large number of cloned human or rodent CNS receptors, channels, and transporters through the NIMH PDSP program (<http://pdsp.cwru.edu/pdsp.htm>). Services include: receptor binding assays, development of assays for molecular targets, and functional assays to determine effects on second messengers, channels, and transporters. A new addition to the program is a searchable database that provides affinity constants at various receptors for nearly two thousand compounds (<http://pdsp.cwru.edu/pdsp.asp>).

CONTRACT CHEMICAL SYNTHESIS. The NIMH currently synthesizes certain novel or difficult-to-obtain psychoactive compounds, maintains a repository, and distributes compounds and reagents for use in basic and clinical research relevant to mental health through the Chemical Synthesis and Drug Supply Program (<http://www.sri.com/pharmdisc/NIMH.program.html>). The repository contains ligands for CNS receptors, radiolabeled compounds for autoradiography, unlabeled precursors for PET and SPECT radiotracers, biochemical markers, drug analogs and metabolites, and reference standards. Compounds are available through an online searchable catalog.

The Chemical Synthesis and Drug Supply Program also has the capability to provide bulk manufacturing (GLP and GMP synthesis) of promising compounds, especially novel PET and SPECT ligands, for toxicology and safety studies.

MOUSE BEHAVIORAL PHENOTYPING. The NIMH currently supports efforts to generate mutant mouse strains (through ENU mutagenesis) and distributes these strains to the scientific community through the Mouse Neuroscience Phenotyping and Distribution Center. This resource serves

to enhance the identification of novel drug targets and the testing of novel compounds. The program could also permit the development of new assays for testing novel therapeutics through the exploratory and development grant mechanism (R21).

BIOLOGICAL MARKERS. The NIMH has initiated activities to foster the identification and validation of biological markers in multiple domains (e.g., imaging, cognitive, behavioral, and genetic) in mechanistic studies of disease pathogenesis and treatment. Several recent program announcements have called for ancillary mechanistic studies of novel biological markers for diagnosis, prognosis, disease activity, or treatment response using patients, patient materials, or information from multisite clinical trials in pediatric and adult populations (<http://grants.nih.gov/grants/guide/pa-files/PA-01-043.html>; <http://grants.nih.gov/grants/guide/pa-files/PAR-00-095.html>).

CLINICAL EFFECTIVENESS TRIALS. The NIMH currently supports several large-scale clinical trials to assess the effectiveness of marketed drugs for the treatment of mental disorders. Three ongoing trials for the treatment of mood disorders include 1) the Treatment for Adolescents with Depression Study (TADS) (<http://www.nimh.nih.gov/studies/tads.cfm>), 2) Sequenced Treatment Alternatives to Relieve Depression (STAR*D; <http://www.edc.gsph.pitt.edu/stard/>), and 3) the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD; <http://www.nimh.nih.gov/studies/stepbd.cfm>). This initiative will serve to develop a clinical trial network in mood disorders.

Specific Suggestions for NIMH Efforts in Drug Discovery and Development

The limiting factor in drug discovery globally in all areas is the available knowledge base. Basic research focused on an understanding of the biology of severe mental illnesses is pivotal to advances in therapeutics. Effective drug discovery requires knowledge of drug targets that are relevant to the underlying pathophysiology. The development of protease inhibitors for HIV/AIDS, gamma secretase inhibitors for Alzheimer's disease, and tyrosine kinase inhibitors for chronic myelocytic leukemia were derived from the elucidation of fundamental pathophysiologic mechanisms that could be targeted for drug therapy. The substantial speed with which these areas of medicine were able to translate basic advances to the clinic demonstrates what is possible for the treatment of major depressive disorder, bipolar disorder, and other mood disorders, if and when their pathophysiologic mechanisms are well defined and rational therapeutic targets follow. As noted earlier, to date the discovery of drugs for mood disorders has its roots in basic research on novel mechanisms of action,

careful clinical observations of the effects of psychoactive compounds, and serendipity (Vetulani and Nalepa 2000).

How Can Basic Research Be Optimized for Drug Discovery by NIMH Initiatives?

PROJECT FUNDING FOR BASIC NEUROSCIENCE RESEARCH. Basic research aimed at understanding disease biology and the discovery of "drugable" targets needs to be promoted through increasing R-O1 funding in this area, using RFAs for this goal, and perhaps most importantly funding riskier research. Incorporation of creative and novel disease models needs emphasis in the RFAs. Innovative formulations of mechanisms as models to explore novel disease targets need a forum. An articulated focus on innovation, in both R-O1-type and SBIR-type mechanisms, in the models being tested and in the methodologies incorporated are equally important. This will involve an emphasis on the development of new and pathophysiology-based animal models for mood disorders, especially mouse models, because these will most easily be able to capture an advantage from modern genomics. Behavioral characterization of genetically altered mice is essential.

Incentivizing the use of modern molecular tools, many of which are now or will be developed by NIMH, may bring faster progress. Capitalizing on public drug repositories, drug databases, advancing behavioral characterization of genetically altered mice, application of powerful DNA array, and proteomic techniques are all likely to advantage discovery. Strategies to prioritize these new directions within NIMH should be considered.

Of some importance would be a central NIMH office to administer and coordinate these activities to fully deliver a programmatic advantage. Drug development has been an undervalued area of mood disorder research for so long that a "remedial" focus may be helpful.

CENTER FUNDING FOR DRUG DEVELOPMENT. A complementary mechanism to stimulate innovation in the drug discovery process is not only to invest in R-O1 research, but also to emphasize multidisciplinary centers that have the dual goal of elucidating pathophysiologic mechanisms of mood disorders and developing targets for drug discovery. Such centers might be based on the Conte model, but also have their success ultimately based on the degree to which proposed studies clearly articulate hypotheses about disease pathophysiology and propose and test targets for drug discovery. These model centers, directed toward discovery in drug targets and treatment mechanisms, would need to facilitate the application of new insights from basic neuroscience to innovative treatment discovery. As such, successful centers would include basic and clinical scientists working interactively to bring clinical observations to the bench and basic insight to the

clinic. Innovation and risks should not only not be penalized, but should be considered essential for such centers.

The current model for a center needs to address many interwoven needs ranging from training of basic and clinical researchers, technology development, and infrastructure investments to targeted research. Single hypotheses are most appropriate for program project applications, whereas centers should support and stabilize a cadre of interactive investigators whose research includes basic and clinical dimensions and may in many cases take the form of “discovery-based” research as opposed to “hypothesis testing.” This is particularly true in stimulating the flow of ideas between branches of neuroscience that can be artificially segregated by department rather than fundamental brain mechanisms. Other institutes such as NCI and National Institute of Diabetes and Digestive and Kidney Diseases have made strategic use of general center mechanisms to develop promising research areas, recruit investigators by supporting intensive core facility development, and encourage local investments in basic and preclinical model investigation. The perception of many outside the NIMH is that the center mechanism currently in place at the NIMH is too narrow in its mission.

SMALL BUSINESS GRANT FUNDING FOR DRUG DEVELOPMENT. The NIMH has a successful SBIR/STTR program. This program has been particularly valuable to many start-up biotechnology companies. With the current funding available, the greatest strength of the SBIR/STTR program is to provide support for pilot proof-of-concept (Phase 2) studies. To increase the level of interaction or involvement of the NIMH with industry, the amount of SBIR funding should be increased. This can be achieved by an increase in the funds available for Phase I and Phase II SBIR grants or by the institution of a Phase III grant for the continuation of successful programs.

Other vehicles of funding should be examined as alternatives to the SBIR/STTR program and used to foster closer collaboration between NIMH and industry. The goal is a true collaboration in which scientific expertise from each group, contributes to projects of mutual interest. One representative mechanism may be to institute a model similar to the National Cooperative Drug Discovery Groups (NCDDG) that exist within NCI. These programs have at their core substantial funding available for a collaboration between government, an academic institution, and industry. At funding levels of \$1 million per year for up to 5 years, these programs provide realistic levels of support to advance drug discovery substantially.

At the moment, in addition to the financial gain, SBIR and STTR funding have an important qualitative benefit to industry. Projects that successfully go through NIMH peer review and achieve funding receive credibility both with scientists and investors alike. This validation of a research

project, the proof of concept of a novel mechanism, or the introduction of a novel yet risky technology greatly benefits the reputation of a small company. With a validated proof of concept behind a drug discovery program, partnership with major pharmaceutical companies becomes easier, allowing novel ideas and mechanisms to be explored in the development of novel therapy.

How Can Clinical Research Be Optimized for Novel Drug Development?

EARLY CONCEPT TESTING OF PROBES USING NOVEL DRUG PROBES. The NIMH should establish a program of early drug development that conducts proof of concept studies of innovative agents in mood disorder treatment. Drugs and strategies exist that have been hypothesized to possess a therapeutic benefit in a variety of psychiatric disorders but that have been inadequately tested. Many of these agents are actually used in clinical practice in the absence of compelling clinical data (e.g., the use of psychotomimetics to augment SSRI response in depressed patients). For those drugs, a definitive concept-testing study would provide the needed evidence to appropriately influence clinical practice. In testing other putative antidepressants or antimanic drugs, important hypotheses regarding the role of a particular neurotransmitter or neuromodulatory system can be tested. It is expected that positive results from NIMH-sponsored proof-of-concept studies would encourage industry to invest in Phase II/III programs. Concomitantly, negative results would have the benefit of ruling out hypotheses that have lingered in the field for decades.

The identification of putative therapeutic candidates is an initial challenge. Sources of drugs can include 1) drugs approved for another indication, 2) off-patent generic drugs, 3) new compounds developed by biotech pharmaceutical companies, 4) new compounds available through large pharmaceutical companies for other indications, and 5) drug probes, developed for concept testing through small academic or government programs. Some of these categories are far fuller and easier to bring forward than others, especially given issues of intellectual property rights. In the case of generic drugs, clinical testing is straightforward. Collaboration with small companies who possess interesting compounds is done in other NIH institutes. Hence, legal and financial precedents exist for such partnerships. In fact, there are substantial advantages to companies who partner with the government for proof-of-concept studies rather than large pharmaceutical companies in that a positive trial can substantially increase the asset value of their product before they have to partner with a major pharmaceutical company. Direct collaboration between the NIMH and large pharmaceutical compa-

nies to facilitate the development of new compounds or seek new indications for approved compounds can prove more problematic, yet such relationships are far from impossible.

TRAINING AND SUPPORT OF CLINICAL SCIENTISTS. Programs attempting to attract competent and well-trained physicians to enter mental health research have thus far not been successful. Disappointingly, the numbers of committed physicians entering research in brain diseases have been shrinking. The shortage of bright and motivated young physicians in the field of clinical research is remarkable. Just at the point when basic neuroscience is creating opportunity in mood disorders, it seems that the brightest and best young physicians elect other medical disciplines. Consequently, the creative translation of basic neuroscience into clinically feasible treatment regimens, let alone their competent testing, is sorely compromised.

The NIMH needs to address this shortage of clinical research scientists in an effective manner. One could speculate that funded training programs, educational loan reimbursement programs, effective advertisement of clinical roles, and an enhanced “reputation” for clinician-scientists might all be effective. Indeed, an NIMH-sponsored special panel to articulate the issues and to propose specific and feasible remedies was held recently. Already, the loss of a generation of clinical scientists can be seen and felt in academic psychiatry and neurology departments around the country, as well as in industry.

CLINICAL TRIAL NETWORKS. With the identification of drug candidates and concept testing, a need will arise for effective and efficient clinical trial networks, capable of large multisite clinical trials. Such networks will be most valuable if they are composed of optimal trial sites with trained and experienced staff at those sites. The current structures of the NIMH Effectiveness Trials Networks in Depression and Bipolar Disorder will surely be the nidus for broader NIMH-sponsored Clinical Trial Networks.

The goals, resources, administration, and focus of a Clinical Trials Network in Mood Disorder Therapeutics need careful consideration. Experience from other institutes and from current NIMH initiatives can be examined, along with the unique requirements of mood disorders as a disease focus. Techniques to attract the best clinical scientists in the field without jeopardizing other NIMH-funded projects needs to be considered. This topic may also be a part of a special panel work group to draw together models for such networks in the area of mental health research.

RESEARCH-RELATED BENEFITS OF A CLINICAL TRIALS NETWORK. Although the need for new therapeutic agents to treat affective disease would be the driving force

behind clinical trial networks, fostering such networks by the NIMH would inevitably yield additional benefits. The question of the appropriate diagnostic or symptom-constellation criteria for a particular treatment would certainly be addressed. The identification of effective drug treatments for symptomatic subgroups of depressive syndromes could prove an important impetus to new methodologic approaches to clinical trials. The putative multigenic etiologies of neuropsychiatric diseases and the increasing likelihood of linking particular genetic, molecular, and cellular pathways with specific behavioral or neurochemical phenotypes encourage this approach already. Clinical phenotypes (rather than diagnostic categories) may prove targets for drug development in the future. Moreover, the more technical but important aspects of clinical trial design would necessarily receive attention, including appropriate subject populations to answer a clinical question, optimal length of trials, optimal use of placebo designs, and evaluation of surrogate markers for drug action or optimal drug dose to advance new drug development.

The generation of new, more precise psychometric measures would be another benefit to the field. The development of new rating scales could be encouraged, and their validity and reliability could initially be tested as secondary measures in other trials. Importantly, biological measures that could serve as surrogate markers for clinical response could be introduced. Obviously the development of new scales, more sensitive ones, or biological markers of clinical response would have the long-term consequence of improving the efficiency of subsequent drug development.

Clinical trial networks would necessarily have to address directly the myriad problems in clinical trials noted here, including but not limited to high placebo response rate, optimal illness populations, high subject dropout rates, and imprecise symptomatic outcome measures, perhaps with a series of focused methodologic experiments. Because these problems surely contribute to the unacceptably high rate of failed trials and imprecise outcomes in mood disorders, the problems need effective and timely solutions. Solutions to these critical clinical trial problems would be a service not only to government and academic research but to industry-based drug development efforts as well.

EMPHASIZING SPECIAL POPULATIONS. The evaluation of drugs for mood disorders in all populations of use, especially children and adolescents, is a recommendation of the FDA and universally espoused. The ethical issues of such trials have been debated and a consensus has been reached; however, because pediatric drug trials in mood disorders have not been widely implemented, the clinical methodology for multicenter trials in children requires

attention. Differential diagnosis of mood disorders in children can be challenging; outcome measures, even symptomatic ones, need evaluation; likewise, simple design features such as subject number and study duration, concomitant medications, and diagnostic diversity all need defining. In addition, a focus on other special age groups, including the elderly and their special treatment requirements, is needed.

Mood disorder diagnosis and treatment studies in ethnic subpopulations in the United States and worldwide is of great importance. An abundance of methodologic issues, many of which are ill defined, plague these studies. More significantly, these kinds of studies are done far too infrequently. Moreover, actual therapeutic trials in racial populations are also lacking, even though their importance can be predicted from known racial differences. Metabolic differences lead to pharmacokinetic differences across populations and probably to neurochemical changes as well, both of which are likely to affect treatment response. Pharmacogenetic markers of response also differ across ethnic groups as well. In today's push toward globalization, this area of pharmacology is a critical one.

What Are the Optimal Tools to Stimulate Drug Discovery?

FACILITATING ACCESS TO DRUG REPOSITORIES AND PUBLIC DRUG LIBRARIES. Despite the paucity of rational drug discovery targets in mood disorders, good hypotheses exist. An obstacle to testing many hypotheses, basic and clinical alike, derives from the absence of "probe" molecules to interact with target brain proteins. Chemical libraries consisting of synthetic and natural products are valuable assets for drug discovery programs. Ultimately, the library could serve as a source of compounds deliverable or available to investigators. An additional consideration is to have the NIMH fund efforts using medicinal chemistry resources already developed within the institute to generate libraries of compounds directed at examining known pharmacophores; these can be made available through the NIMH Chemical Synthesis and Drug Supply Program. If a library of "CNS-active" molecules could be collected, cataloged, and made available for funded science, this would allow a concentrated effort on generating interesting diverse molecules that may have utility as starting points for drug discovery programs.

ASSIMILATING A DRUG DATABASE. Similarly, the NIMH could maintain a database of information on new compounds and reagents that can be made available to facilitate drug discovery. This reagent database would direct investigators to laboratories where they could obtain new antibodies or ligands, well before they are commercially available. This proposed repository of information

could be an add-on to the existing NIMH Chemical Synthesis and Drug Supply Program repository. The Web-based database of reagents for the current NIMH synthesis program needs to be integrated with other databases, perhaps that at Case Western Reserve University (CWRU), to provide relevant information about biological activity in a searchable manner. It would be helpful to identify existing data on the selectivity and specificity of the compounds in the library through hyperlinks either to references or contract databases. The goal should be to have a single user interface that would allow investigators to identify either a target such as "5HT₇ receptor" or a ligand class such as "phenothiazine" and then obtain all the information as to compound availability, activity, or structural variants.

FACILITATING AVAILABILITY OF DISEASE TISSUE FOR STUDY OF DRUG TARGETS. Promoting the availability of high-quality human postmortem tissue for the field from carefully diagnosed cases of mood disorders and matched healthy control subjects would provide a substantial contribution to pathophysiology studies. This could be accomplished either with or without a further NIMH investment into federally funded collections. An ongoing inventory of available tissue, with tissue characteristics, diagnosis, source, and supervising scientists would be an obvious start. Common standards for collection and diagnosis could be developed by a group of experts. A facilitation of high-quality scientific collaborations across laboratories with the application of cutting-edge technologies to well-collected and characterized human tissue would be the hope. If the NIMH had its own tissue source, then it could direct collection characteristics and provide that tissue to new investigators with cutting-edge technologies, potentially contributing to new information about disease mechanism and drug targets.

For example, the application of regional expression profiling to human postmortem mood disorder tissue for the purpose of drug target development could be advanced by the NIMH. DNA microarray technology enables the generation of large data sets contrasting gene expression from disease with nondisease brain tissue on a regional basis; the NIMH could produce publicly available regional expression libraries for mood disorder investigators. The opportunity to develop and make these data sets public could enable a broad cadre of investigators to use the complex experimental results for subsequent hypothesis testing toward the goal of developing drug targets. If the NIMH would sponsor this work, it could ensure optimal starting material, consistent methodology, and broad application of data-analytic and mining techniques to maximize information yield. One could predict an optimal scenario: first an effort in new treatment development could begin based on data from a regional expression

library to formulate a novel hypothesis of mood disorders; investigators could test the hypothesis in appropriate postmortem tissue itself, then launch a novel development plan for a mood disorder diagnosis. One could conceive of this as being completed under grant or contract mechanisms. The related task of developing high-quality regional cDNA expression libraries could also be similarly accomplished, with equivalent advantage to the field.

What Is the State of Somatic Treatments for Mood Disorders?

In many respects the study of somatic treatments is comparable to that of other interventions for mental disorders using clinical trials methodology, including specified treatment parameters, duration, and standard outcome measures; however, certain characteristics of somatic treatments distinguish them, to varying degrees, from standard pharmacologic and psychotherapeutic interventions and present special challenges to the performance of scientific research.

Because of the relatively invasive nature of some somatic therapies, their use is skewed toward a more severely ill mood disorder population. For example, ECT is specifically indicated in cases of severe depression accompanied by psychosis or catatonia. This also means that a disproportionate number of individuals available for study or clinical treatment using electroconvulsive therapy or another relatively invasive treatment modality, such as vagal nerve stimulation (VNS), will be treatment refractory at presentation. This can work against the development of new somatic treatments, in which the classical active versus control condition paradigm may fail to show sufficiently robust efficacy for a new treatment when typical, moderately ill patients may not be available for study with a novel but invasive treatment modality.

The need to study very ill patients also means that it is difficult to establish a medication-free baseline, which would be ideal to study the true effects of a somatic intervention and essential for meaningful mechanism of action research. This has been less of an obstacle to pharmacotherapy research, for which the use of multiple medications has become the norm in severe mood disorders. The only controlled trial of ECT in mania, for example, was published more than a dozen years ago (Rudorfer 1989). Some investigators have moved instead toward combined treatment studies of somatic treatments plus drug treatment.

Indeed, in some cases there is no agreement, scientifically or ethically, on an appropriate control or placebo condition for somatic treatment research. A sham ECT condition, involving the induction of general anesthesia with no electrical stimulation, was used in more than a

dozen studies in the United Kingdom during the late 1970s and 1980s but has never been used in the United States due to the unacceptable risk of anesthesia in the absence of possible benefit to the individual patient. Much of the light treatment literature is clouded by questions about the unconvincing (e.g., dim red light) nature of the putative control condition. More recent research (e.g., by Eastman) using sham negative ion generators as a more plausible control condition have helped establish the efficacy of light treatment in winter depression.

Current Research and Future Directions

ECT. Electroconvulsive therapy continues to be the primary treatment for medication-resistant depression despite developments in new medications and other somatic treatments including vagal nerve stimulation (VNS) and transcranial magnetic stimulation (TMS). Although ECT is associated with significant side effects and other drawbacks such as social stigma, ECT use in the United States has increased and, with the pressure of containing costs by shortening hospital stays, the use of ECT in general psychiatry will probably continue to increase over the next decade. The following four major areas of research in ECT and other somatic treatments should be supported.

Developing a scientific understanding of the mechanisms of action of ECT. Understanding the mechanism by which an electrical convulsion can exert a therapeutic benefit in depression can support depression research both by decreasing the stigma of ECT and by encouraging the development of new somatic treatments. The NIMH is promoting ECT research (Salzman 1998), but more basic science research is needed. Theories such as the diencephalic hypothesis (Abrams and Taylor 1976; Fink and Ottosson 1980) have been challenged by recent data supporting the anticonvulsant hypothesis (Sackeim 1999). The anticonvulsant hypothesis proposes that the therapeutic effect of ECT is due to the release of endogenous neuropeptides and neurotransmitters that decrease the excitability of the brain. This hypothesis is supported primarily by clinical research and intriguing but sparse preclinical data (Tortella and Long 1985) supporting the theory that when ECT is effective, there is an active inhibitory process shown by an increase in the seizure threshold (Sackeim et al 1986), and electroencephalographic (Krystal and Weiner 1994) and regional cerebral blood flow changes (Nobler et al 1994).

Funding for clinical research should continue to concentrate on developing algorithms to determine the relationship of ECT treatment variables (e.g., seizure threshold) to ECT response or the loss of seizure efficacy during a course of ECT. These algorithms can test theories such

as the anticonvulsant hypothesis and guide clinicians in administering effective treatments. Changes in treatment variables related to response (e.g., diminished CBF in the anterior frontal lobes or an increase in the seizure threshold) may also be investigated to predict relapse.

Optimization of the efficacy of an acute course of ECT. This area has been a focus of NIMH research on ECT, but the results have had a minimal impact on clinical practice, perhaps because there is no currently standardized certification for ECT practitioners. Moreover, much of the data comparing uni- and bilateral ECT has been limited to major depression, and there is a need for data in other treatment groups particularly in acute mania (Black et al 1989; Mukherjee and Debsikdar 1994). Others have also argued for the support of ECT research in special populations including adolescents and individuals with neurologic diseases such as Parkinson's disease, agitation in dementia, and developmental disabilities.

The debate, which has been focused on the efficacy of unilateral versus bilateral treatments, should shift to other areas including electrode placement and ultrabrief pulse frequencies. These treatment modifications have the potential advantage of decreasing ECT-related cognitive side effects, although controlled clinical trials have not been completed (Sackeim et al 1994). These ultrabrief pulse widths (compared with the .5–2 msec used by most practitioners) have the potential advantage of producing a seizure using decreased energy and causing fewer cognitive side effects.

Although the d'Elia is the accepted electrode position for right unilateral ECT, recent trials have supported the use of novel bilateral electrode placements to replace the traditional bifrontotemporal position. There is evidence that bifrontal placement may increase efficacy and decrease cognitive side effects (Bailine et al 2000; Lawson et al 1990; Letemendia et al 1993). Further research is needed to test these electrode placements as well as other novel placements such as the combination of a right frontal placement and a left frontotemporal placement (Swartz 1994).

Minimizing the cognitive side effects from ECT. Research into alternative stimulus electrode placements, stimulus waveforms, and pharmacologic agents (e.g., naloxone, physostigmine, and thyrotropin-releasing factor) to decrease the cognitive side effects of ECT should be encouraged. Clinical studies of acute and maintenance ECT should be carefully designed to examine the effects on cognition.

Optimizing long-term outcome. The NIMH support for studies in continuation and maintenance pharmacotherapy

and ECT after an acute course of ECT that will provide important clinical guidelines for clinicians who are increasingly using maintenance ECT. These studies should include measures to predict relapse in vulnerable populations. Previous studies have shown that medication resistance before ECT is an important predisposing factor in relapse after ECT (Prudic et al 1996). There is preliminary evidence that electroencephalographic morphology and cerebral blood flow may also predict response to ECT and relapse after a course of ECT. Research into the clinical and biological markers of relapse after ECT can have important clinical implications.

REPETITIVE TMS. In contrast to the application of an electrical stimulus to the scalp, as in ECT, a more precisely localized electrical current can be produced within the brain by pulsing a magnetic wave (generated through a coil on the head), which passes undistorted through the skull. The resulting cortical stimulation has been used as a neurophysiologic probe to assess motor function within the cortex.

Over the past decade devices have been developed capable of delivering repeated TMS pulses. A train of TMS pulses, delivered to the left prefrontal cortex repeatedly but at a subconvulsive rate over time daily to an awake and alert patient, has demonstrated antidepressant efficacy in several small open and sham-controlled trials. To date, antidepressant effects have been relatively modest, and few patients have been medication free or followed systematically beyond a 1- or 2-week rTMS treatment trial. Thus, the role of this new modality in the treatment armamentarium remains uncertain. Encouraging further research is a critical need for this noninvasive procedure, which does not require anesthesia and has rarely been associated with adverse effects beyond mild headache.

The growth in TMS research has increased dramatically in the last decade. Most of the studies have included small sample sizes, patients on antidepressant medications, and varying treatment parameters and machinery. There have been a number of obstacles to TMS research including the infinite number of variables (pulse duration, intertrain intervals, stimulation frequency, days treated, site of treatment), difficulties in establishing a true placebo condition, and restrictions on the use of TMS in only the most severely treatment resistant patients. Perhaps the most difficult obstacle has been the lack of funding. Companies manufacturing the TMS machinery are small and have limited resources for the type of multicenter, placebo-controlled studies needed to definitely test TMS.

Despite these difficulties, there is preliminary evidence of an antidepressant effect when TMS is applied to the area of the prefrontal cortex and additional evidence for possible efficacy in mania, anxiety disorders, and schizo-

phrenia. The promise of an alternative treatment for patients who have failed medication that has fewer side effects, is easier to administer and is not associated with the social stigma of ECT is encouraging. Research on TMS has not progressed to the point at which a definitive large-scale trial is warranted. Research should be focused on small grant proposals to determine which technical, clinical, and biological factors predict who will respond to TMS.

There is initial evidence supporting a number of factors that may improve treatment response. Clinical factors that predict improved response include younger age and lack of psychosis. Technical factors influencing outcome include increased number of total stimulations and increased intensity of stimulations relative to the motor threshold. A biological factor predicting outcome includes patterns of glucose uptake on PET scanning. Once these variables have been further clarified, then support for a large-scale clinical trial, using the most efficient technical parameters in a patient population that is designed to benefit from the procedure, will be clearly warranted.

VAGUS NERVE STIMULATION. Vagus nerve stimulation is an effective treatment of refractory seizure disorders that has shown some promise as an antidepressant intervention. It was approved by the FDA in 1997 for selected cases of epilepsy. VNS was first reported to be associated with improved mood in neurology patients and more recently has shown partial efficacy in refractory mood disorders. Although, recently the results of a large multicenter trial has been disappointing. The afferent connections of the left vagus nerve with locus ceruleus, dorsal raphe, and limbic structures are implicated in the putative antidepressant effect of this intervention.

A small, pacemaker-like device is implanted beneath the clavicle, with an attached lead wrapped around the left vagus nerve in the neck. Safety experience with seizure disorder patients has been satisfactory; stimulation of the left vagus nerve has no cardiac effects. In addition, VNS holds promise for the treatment of resistant patients, with the added benefit of improvement that persists over time and may actually show increased benefit during maintenance treatment.

A recent interesting finding on the development of depression in an individual with Parkinson's disease after implantation of a deep brain stimulator in the area of the subthalamic nucleus (Bejjani et al 1999) raises another possible use of somatic treatments in understanding and treating depression. This subject had no history of depression, yet stimulation through specific electrodes precipitated depressive symptoms. This suggests that depression may be hard wired in the brain (Yudofsky 1999). Therefore, in the future, it may be possible to use high-frequency stimulation to modulate circuits involved in

depression; however, deep brain stimulation (DBS) is an invasive procedure, and its use in treating psychiatric disorders is highly speculative. Research in this area should focus on psychiatric symptoms developing in patients with DBS implanted to treat PD and other neurologic disorders.

OTHER MODALITIES. Early observations that many depressed patients with repeated fall and winter depressions benefited from light therapy introduced the idea that the melatonin system is involved in affect modulation. Considerable work has been done in studying diurnal rhythms of melatonin in winter depressions and in phase disorders. Now melatonin and its agonists are being applied not only in sleep-phase disorders but also in seasonal depression and in depression of the elderly. Considerable research is ongoing in this area, covering the basic as well as applied effects of light.

Several small studies have reported antidepressant effects of acupuncture in unipolar major depression. Indeed, a controlled pilot study reported a full remission in 64% of depressed patients treated over 8 weeks with acupuncture (Allen et al 1997). These data formed the critical background for a study of medication-resistant bipolar subjects using acupuncture (Trisha Suppes, personal communication) now in progress.

The Contribution of Human Brain Imaging Techniques to Disease Mechanism Study, Drug Target Identification, and Drug Development

Overview

Biomarkers are commonly used in fields of medicine other than psychiatry to aid in diagnosis, to determine treatment, and to monitor the efficacy of therapy. A common example of a biomarker is the cholesterol test, which is used as an indirect or sometimes called "surrogate" measure of increased risk for future cardiovascular disease. Thus, measurement of serum cholesterol is recommended in some subjects (including middle-aged individuals and those at increased genetic risk) who are completely asymptomatic. Elevated cholesterol levels, even in the absence of signs or symptoms of disease, are justification for preventive treatment. Furthermore, cholesterol levels are repeated during treatment to ensure an adequate and sustained response. The field of psychiatry lacks any such comparable biomarker to measure mood disorders. In analogy to the cholesterol test, an ideal biomarker in psychiatry would detect abnormalities before the manifestations of a depressive or manic episode (i.e., before the physician or even the subject could predict the onset of symptoms). It also should provide critical information to

direct specifically targeted therapies, including psychosocial as well as pharmacotherapies, and it should be used to monitor the efficacy and sustained effect of those interventions. Such a biomarker would not supplant current psychiatric evaluation and direct patient contact. Instead, similar to the cholesterol test, a psychiatric biomarker would be used in conjunction with direct patient contact in multiple roles of education, prevention, and therapy.

Current Status

Biomarkers for mood disorders can be roughly divided into four groups, with examples and a representative review article provided for each.

PERIPHERAL. Examples: urinary and plasma levels of catecholamines, plasma cortisol level, densities of serotonin transporters on platelets (Review: Holsboer 2000).

CNS NEUROCHEMICAL. Examples: PET and SPECT measurements of receptors or magnetic resonance spectroscopy (MRS) measurements of GABA and glutamate. (Review: Fujita et al 2000).

CNS FUNCTIONAL. Examples: measures of local neuronal activity determined from EEG, ERP, magnetoencephalogram, and functional magnetic resonance imaging. (Review: Drevets 2000).

GENETIC. Examples: DNA markers of risk factors or individual genes that cause mood disorders. (Review: Sanders and Detera-Wadleigh 1999).

The succinct summary of the current status of biomarkers in the field of mood disorders is that no strongly predictive measure is currently available; however, recent developments in neuroimaging (especially neurochemical imaging with PET and functional imaging with functional magnetic resonance imaging [fMRI]) offer great promise both to gain better understanding of the underlying pathophysiology of mood disorders and to develop useful biomarkers to evaluate drug response (Innis et al 2001).

Biochemical Markers

The majority of work to date on biomarkers has examined peripheral markers, including catecholamine levels in plasma and urine, platelet markers such as the serotonin transporter, and plasma measures of HPA axis activity (e.g., cortisol and adrenocorticotropic hormone). The studies on peripheral biomarkers in mood disorders were initially quite popular and well received by the research community; however, a strong counterreaction to the catecholamine and platelet measures subsequently developed, in large part because they did not clearly reflect CNS

activity or function. In contrast, studies of the HPA axis (including plasma cortisol) have continuously flourished, showing the role of extra-hypothalamic areas in regulating and being affected by cortisol. Neurochemical imaging in the brain with ligands (i.e., PET and SPECT) and with spectroscopy (MRS) will almost certainly overcome limitations of the peripheral chemical biomarkers by examining chemical activity directly in the brain. For example, promising preliminary studies suggest that depression may be associated with altered levels of several serotonergic markers, including reduced density of the serotonin transporter, 5-HT_{1A} receptors, and 5-HT_{2A} receptors. Most of the ligand neuroimaging studies in mood disorders have been limited to the serotonin system and have used relatively small sample sizes. Two major ways to expand these techniques in the future would be to examine a much wider number of targets and to use much larger sample sizes to accurately capture the diversity of subsyndromes and components of illness reflected in patients with mood disorders.

Functional Markers

New methods from cognitive and affective neuroscience provide an unprecedented opportunity to use noninvasive techniques to examine the function of brain circuitry underlying disturbances of cognitive and affective processing in affective disorders. These methods take the general approach of defining behavioral constructs and developing valid behavioral probes that are incorporated into neuroscientific studies to reveal activity in the relevant brain networks. Reliable methods now exist to examine the brain circuitry associated with attentional and executive functions and to define the abnormal cerebral activation patterns in unipolar depression and bipolar disorder. Conceivably, a “normalization” of these abnormal cerebral activation patterns could define drug activity. Similarly, reliable paradigms have been developed to examine activity in subcortical and limbic circuits associated with processing reward, threat, and other kinds of emotionally relevant information. Deficits in these functional domains are widely reported to be present in individuals with affective disorders.

Despite the dramatic increase in research into the neural basis of normal cognitive and emotional processes, not enough has been done to apply these methods to the investigation of affective disorders. However, the potential for these tools to provide insights into pathophysiology and mechanisms of action of treatment, as well as to serve as predictors of outcome, is considerable, and the noninvasiveness and potential wide availability of methods such as fMRI and high-density ERP make these tools especially attractive. Facilitating the application of cognitive and

affective neuroscience based imaging methods for use as potential biomarkers could lead to significant progress in the diagnosis and treatment of affective disorders.

Target Goals and New Initiatives

NEW LIGAND DEVELOPMENT. Tremendous opportunities exist for the application of PET and SPECT imaging in studies of the pathophysiology and treatment of CNS disorders, but relatively few radioligands are currently available for functional imaging of target molecules implicated within normal brain function and in CNS disorders. Thus, we recommend that the NIMH work within its intramural and extramural programs to develop new ligands but then facilitate their dissemination for use by all researchers in the field. These ligands are likely to be useful for several purposes: 1) to better understand the abnormal chemical processes that underlie mood disorders; 2) to be used in conjunction with the development of new therapeutic agents to determine where they work in the brain and to guide initial dosing of such agents; and 3) to be used as central biomarkers of the illness, potentially to predict onset of symptoms, to monitor the progression of the disease, and to assess the efficacy of therapy.

Effective partnering with industry for ligand development will be immensely valuable. The pharmaceutical industry has valuable chemical expertise and an array of well-characterized molecules that are the products of a large investment in research and development of medications for CNS disorders. These molecules (marketed and nonmarketed) could be adapted as PET or SPECT ligands to visualize brain targets (e.g., receptors, intracellular messengers, disease-related proteins) of mutually beneficial interest to pharmaceutical companies, academic investigators, and the NIH.

The NIMH has already begun to assess the need for, and its potential role in, the development of new ligands. A 1-day panel on this topic was convened in January 2001 and included representatives from academic sites, the FDA, pharmaceutical companies, and representatives from several NIH branches (<http://www.nimh.nih.gov/research/confsummaries.cfm>). This panel recommended several excellent ways in which NIMH could foster ligand development, including the following: 1) partnering with industry, including possible means to address intellectual property rights issues so that they do not impede the process (Innis et al 2001); 2) issuance of an radio frequency ablation (RFA) specifically for the development of radioligands; 3) establishment of an annual meeting of a neuroimaging consortium (industry, academia, NIH, and the FDA) to continue the exploration of means to stimulate ligand development.

Certainly, ligand imaging need not completely supplant all other peripheral biomarkers. Rather, useful peripheral

measures such as cortisol should be obtained in conjunction with the imaging studies. This combined analysis will better help to understand the significance of each and potentially help to dissect subsyndromes or aspects of the illness such as cognitive dysfunction and mood dysregulation.

FUNCTIONAL BIOMARKER DEVELOPMENT. The non-invasiveness of fMRI, its wide availability, and its ability to engage specific brain circuitry associated with discrete, functionally relevant aspects of affective disorders make it a particularly promising tool for biomarker development. For some functional measures (e.g., attention and executive functions), paradigms already exist for which validity and reliability have been established. In other areas, particularly the affective domain, further development and validation are needed. A consensus conference sponsored by the NIMH and focused on the development of behavioral measures of affective processing and their integration into functional imaging studies could facilitate this process. The rapid validation of these methods would also be enhanced if incentives were offered to “add on” these measures to ongoing multicenter treatment studies. An RFA could facilitate this process.

Pharmacogenetics and Its Contributions to Drug Discovery and Drug Utilization

Current Status of the Field

Pharmacogenetics seeks to find DNA markers for medication treatment outcome (Roses 2000). The current status of pharmacogenetics in mood disorders is relatively limited. There are three published reports in the United States and Europe indicating that the allele for the short form of the serotonin transporter promoter is associated with poor response to SSRIs (Pollock et al 2000; Smeraldi et al 1998; Zanardi et al 2000). Homozygotes for this allele are found at a frequency of approximately 25% in Caucasian populations. There is also one report from Korea that the long form of the transporter promoter, which is less common in that population, is associated with poorer responses to SSRIs (Kim et al 2000). In another study (presented by Murphy et al at ACNP 2000 and NCDEU 2001), the APOE ϵ 4 allele was associated with rapid response to mirtazapine but not paroxetine in elderly patients. All of these studies have used conventional polymerase chain reaction (PCR)-based genotyping for single polymorphisms. In the Murphy et al mirtazapine-paroxetine study, a commercially available microarray was used to query for 16 CYP2D6 alleles that affect antidepressant metabolism. The results showed very modest effects of intermediate and poor metabolic alleles on ability to tolerate mirtazapine and paroxetine during long

term treatment. In another study, Murphy et al (2001) used CYP2D6 oligonucleotide microarrays to predict nortriptyline drug levels at steady state in patients with geriatric depression. To our knowledge, these are the only presented or published data on pharmacogenetics in depression. In bipolar disorder, the short form of the serotonin transporter protein promoter has been associated with mania induced by proserotonergic medications (Mundo et al 2001). There are no studies relevant to mood disorders in which large numbers of single nucleotide polymorphisms (SNPs) are queried to identify chromosomal regions potentially harboring new antidepressant pharmacogenes.

Goals

IDENTIFICATION OF POLYMORPHISMS ASSOCIATED WITH TREATMENT RESPONSE. One goal for pharmacogenetics is to have a set of polymorphisms that predict relative response and tolerability to specific classes of antidepressants or to specific members of classes. The suite of genetic variants could also help predict which patients need longer term maintenance treatment. Identification of polymorphisms predicting medication intolerance could help avoid unnecessary exposure to various drugs. Pharmacogenetics could also stimulate the development of new agents with even more specific or targeted modes of action. Many polymorphisms could be identified in public databases using candidate loci chosen based on current understanding of antidepressant mechanisms of action.

GENOTYPING MECHANISMS. A secondary goal would be identification of a high-throughput platform for determining genotypes economically in large numbers of patients (Jain 2000). This could lead to screening of a large number of SNPs throughout the genome to identify pharmacogenetic markers not previously associated with known antidepressant mechanisms.

NIH ROLE. There is a potential downside risk for some pharmaceutical companies in that they could potentially lose market share if markers are identified that predict nonresponse or intolerance to a product. Therefore, it is a unique opportunity and likely essential for the NIH to take a lead role in this area. Partnerships with industry will be predictably easier to effect when possible predictor genes for specific drugs are already identified.

There are a number of timely questions that should be considered:

- Should all treatment studies funded by NIMH routinely collect blood for DNA?
- Should pharmacogenetics be routinely added only to large-scale studies (e.g., to Star-D, CATIE)?

- What types of funding mechanisms should be used to support such research?
- Should DNA extraction or genotype analysis be done centrally? Distributed across sites?
- How should the possibly differing views regarding issues of ethics or informed consent be resolved?
- What platform(s) should be supported for high-throughput genotyping efforts?
- How should data involving hundreds or thousands of polymorphisms in thousands of patients be analyzed?
- How can the impact of ethnicity on pharmacogenetic outcome be addressed in current clinical trial designs? Are new designs needed?

Recommendations for Facilitating Research in Pharmacogenetics

EDUCATION. First, there is a need to educate the field on pharmacogenetic studies, including optimal study designs, identification of candidate genes relevant to psychiatry, statistical strategies to analyze data at multiple loci; the field should also be informed about which studies are currently funded. Although the technology exists to determine thousands of SNPs rapidly in large numbers of patients, there are no established statistical techniques for analysis of massive data sets in which issues of multiple statistical testing become of paramount importance. An effort should be led by the NIMH to advance pharmacogenetic methodology and analysis and should include a series of workshops as well as a possible Web site. Specific guidelines for how to design and conduct pharmacogenetic studies should also be developed by the NIMH and included on the Web site.

The NIMH can play a role in deciding on those genes that should first be explored in pharmacogenetic studies. This could initially include several hundred candidate genes, and an interdisciplinary conference format could be organized to develop the candidates. Current lists of candidate loci and polymorphisms (Cravchik and Goldman 2000) need to be regularly updated due to the constant influx of new information on genetic variability in public databases. Consideration should be given to interacting with groups—public and private, contracting when necessary—who may have important data on DNA sequence variants in the genes of interest and allele frequencies in various ethnic populations. This information should be made available to interested scientists working in the field.

DATA-MINING OF EXISTING DATABASES. The NIMH should support efforts to mine existing DNA sequence databases for polymorphisms already identified in genes of interest (Pfof et al 2000). Databases such as those established by the SNP Consortium, HGBASE, the

NIGMS Pharmacogenetics Research Network, and NCBI dbSNP contain thousands of SNPs that could be immediately used for pharmacogenetics studies in mood disorders. The NIMH should support the development of point-and-click software tools designed to provide easy access to SNP sequences at individual loci, as well as available information on PCR primers, amplification protocols, and allele frequencies. Collaborations with existing bioinformatics companies in the process developing database mining tools should be supported. Efficient mining of existing SNP databases could result in tremendous savings of time and money otherwise spent in redundant DNA sequencing, assay development, and population genetic studies.

TECHNOLOGY DEVELOPMENT OF PHARMACOGENETICS. Haplotype analysis is likely to become important in pharmacogenetic prediction (Judson et al 2000). Both DNA database mining and de novo sequencing efforts should be directed toward identifying sets of alleles forming common haplotypes (alleles inherited as a unit) at important candidate loci. This may substantially increase pharmacogenetic predictive power because multiple SNPs that occur together in most individuals may have an additive effect on phenotype (Drysdale et al 2000).

The NIMH should support the development of technology to speed genotyping at specific loci relevant to psychiatry, including microarray technology and other high-throughput platforms (Jain 2000). This could be then made available to investigators, possibly through NIMH centers designed to provide this core service, or industry subcontractors. At present, there are variety of competing platforms for high-throughput genotyping, and it is unclear which, if any, will emerge as the dominant technology. It is likely technologies will be identified that are best suited for a particular pharmacogenetic application. For example, microarray platforms may be best suited for scoring large numbers of SNPs on a relatively small number of patients (Fan et al 2000), whereas other techniques with lower per patient costs may be suitable for scoring a few SNPs on very large numbers of patients. The NIMH should support studies to define the application of these emerging technologies.

Large-scale clinical trials supported by the NIMH should be encouraged to develop and include pharmacogenetic protocols. Specific polymorphisms should be tested across studies. Efforts should be made to encourage collaboration and reduce duplication. Current NIMH trials such as CATIE and Star-D have a naturalistic design that is well-suited to testing treatment algorithms in real-world clinical settings; however, these designs involving large numbers of clinicians, study sites, variability in actual treatment regimen among patients, and population stratification may lack the necessary homogeneity necessary to

detect subtle pharmacogenetic effects. During the planning stages future algorithm-based clinical trials should consider study design features specific to pharmacogenetics.

Strategies are needed to incorporate more ethnic minorities in pharmacogenetic trials. Allele frequencies vary across populations, and identical polymorphisms may have different effects depending on genetic background; however, haphazard inclusion of minorities in sample populations is likely to confound results due to population stratification and yield insufficient numbers of minorities for meaningful statistical analysis. In the planning stages, future pharmacogenetics studies should specifically target ethnic recruitment with statistical power considerations taken into account. The NIMH should provide specific funding for recruitment of minorities into pharmacogenetic trials. This should include support for recruitment specialists who are skilled in outreach to minority communities where traditional attitudes toward blood samples, heritability, and mental illness may be at variance with participation in clinical pharmacogenetic studies.

Ethical Guidelines Leadership

The NIMH and other institutes should support efforts to develop uniform standards for informed consent and guidelines for utilization of DNA samples in multiple pharmacogenetic studies. At present, there are no standards for informed consent for pharmacogenetic studies, and the nature of consent in pharmacogenetics may differ from that for studies of disease-risk genes (Robertson 2001). Standards are also lacking as to how to consent for future studies with stored DNA samples. Standards should be devised that facilitate genetic research in this area while respecting individual privacy. Subcontracts with established clinical research organizations (CRO) to develop uniform informed consent forms and to manage stored DNA data may be a way of rapidly implementing new standards; however, at present most CRO lack experience in pharmacogenetic studies. The NIMH should support interaction of pharmacogenetic researchers with the CRO industry to facilitate this process.

Conclusion

We have attempted to comprehensively review the state of current treatments, and the development of novel treatments, for mood disorders. We have made myriad recommendations, ranging from strategies to increase the discovery of novel molecules to those that will enhance the likelihood of detecting a therapeutic signal in large-scale clinical trials. The leadership of the NIMH must decide which of these many recommendations can be implemented.

This manuscript is one of ten prepared by workgroups under the auspices of the National Institute of Mental Health (NIMH) strategic planning initiative for mood disorders research. Each of the workgroups was given the specific charge to 1) review the state of their assigned area; 2) identify gaps and state a vision of where the field should be going and why; and 3) make general recommendations for NIMH to consider regarding research initiatives that would advance and improve the knowledge and treatment of mood disorders. This document reflects the opinions of the authors and not those of NIMH, but was used in an advisory capacity while the actual strategic plan was developed by NIMH staff. Overall guidance was provided by the National Advisory Mental Health Council.

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