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Discussion

Psychopharmacology: A house divided

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ABSTRACT

Background: Psychopharmacology and psychiatry during the past 50 years have focused on the specificity model in which it is assumed that psychiatric disorders are specific entities which should respond to drugs with specific mechanisms of action. However, the validity of this model has been challenged by the approval of multiple drugs for the same disorder, as well as the approval of single agents for a variety of disorders which have little in common. As an example of this unacknowledged paradigm shift, I will examine the foundation for using antipsychotics in the treatment of depression.
Methods: An extensive literature search of studies investigating various mechanisms of actions of antipsychotics and antidepressants with the goal of identifying neurochemical processes common to both.
Results: The neurochemical differences in these classes of drugs appear to be profound, although several processes are common in both, including some degree of neuroprotection and changes in the epigenome. Whether these common features have any effect on clinical outcome remains in doubt.
Conclusions: While psychopharmacology and psychiatry remain largely committed to the specificity model, it appears that clinicians are prescribing on a dimensional model wherein symptoms are being treated with a variety of drugs, regardless of the diagnosis.

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1. The conflicting goals of psychopharmacology

Psychopharmacology is rapidly becoming a house divided. In one room we find the Molecular Medicine Group (MMG) pursuing the dream of personalized medicine, with the goal of developing drugs based on the genetic profile of the individual patient. If successful, each drug would be used by very few patients, no doubt at a tremendous cost (Dean, 2009). Across the hall we find a Conglomerate of Investigators and Captains of Industry (CICI) on a strikingly different path, relentlessly pursuing US Food and Drug Administration (FDA) approval for the use of drug X in disorders A, B, C, D, etc., many of which have little in common with regard to their pathophysiology, symptoms, and course. Not surprisingly, the CICI has been pushing the FDA for fewer restrictions on the off-label uses of drugs, an effort that has been quite successful, as witnessed by a recent study (Leslie et al., 2009) showing that 60% of antipsychotic medications in the Department of Veterans Affairs Health Care system were prescribed for off-label diagnoses ranging from adjustment disorder to post-traumatic stress disorder.

What are we to make of these deeply contradictory goals? While the goals of the MMG appear to have a rational foundation, the goals of the CICI appear irrational—never mind the financial windfall—given the aims of biological psychiatry over the past 4–5 decades (Andreasen, 1984; Guze, 1989; Insel and Quirion, 2005). These have centered on elucidating the *specific* neurochemical and genetic bases of the major psychiatric disorders as well as the *specific* biological mechanisms underlying the effects of psychotropic drugs. At the same time, biological psychiatry adopted a categorical model of disease, in which there are posited points of demarcation between disorders, both clinically and pathophysiologically. Andreasen (1984) stated this very clearly when she wrote that the biological model "…assumes that each different type of illness has a different specific cause."

Whether the goals of biological psychiatry have been met is another question, since we still have no definitive answers regarding causation, no laboratory studies which will independently validate the diagnosis of any psychiatric disorder, and little consensus on specific mechanisms of drug action. Indeed, doubt has been raised about whether such goals are even possible (Gold, 2009; Paris, 2009). Nevertheless, given these goals, it seems paradoxical that FDA, in conjunction with the CICI, has dramatically expanded the indications for both classes of drugs and individual agents. For example, sertraline has been approved for the treatment of multiple disorders, including major depression, panic, generalized anxiety, obsessive–compulsive, post-traumatic stress, and premenstrual dysphoria. Atypical antipsychotics can now be given for

Abbreviations: ASICs, acid-sensing ion channels; ADs, antidepressants; APs, antipsychotics; βARs, beta-adrenergic receptors; BDNF, brain-derived neurotrophic factor; CRS, chronic restraint stress; CDS, chronic social defeat stress; CREB, cyclic-AMP response-element-binding protein; DMT-1, DNA-methyl transferase 1; DA, dopamine; ECS, electroconvulsive stimuli; ECT, electroconvulsive therapy; GAD67, glutamic acid decarboxylase 67; HDACs, histone deacetylases; NGF, nerve growth factor; nAc, nucleus accumbens; Reln, reelin; SSRIs, selective serotonergic reuptake inhibitors; 5-HTA, serotonin.

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both schizophrenia and bipolar disorder, while aripiprazole is now approved as an adjunctive treatment for major depressive disorder and very recently for the treatment of irritability in autism, as has risperidone. Quetiapine is approved not only for schizophrenia, but as monotherapy for acute bipolar depression, as an adjunct to antidepressants (ADs) in adults with major depression, and as an adjunct to lithium and divalproex for maintenance therapy in bipolar illness. In August 2009 asenapine became the first antipsychotic (AP) to be simultaneously approved for use in schizophrenia and bipolar disorder.

From a different perspective, allegedly specific disorders can be treated with multiple agents. For example, mania can be treated with lithium, divalproex, carbamazapine, lamotrigene, electroconvulsive therapy (ECT), and atypical APs. Bipolar depression can be treated with several atypicals, as well as ADs and ECT, while therapy for major depressive disorder includes vagal nerve stimulation, ADs, APs, cognitive behavioral therapy, and, in the case of treatment-resistant depression, transcranial magnetic stimulation.

A reasonable question follows: how is it, for example, that an allegedly well-defined illness such as bipolar mania can respond to an array of drugs that often have markedly different mechanisms of actions? This approach seems incongruent with the goals of molecular medicine and more generally with the goals of biological psychiatry, which have focused on establishing the specificity of disorders and treatment methods. On the other hand, if one drug can be used to treat 6 or more different disorders, or, if one disorder can be treated with 6 or more different drugs or instruments, why bother with molecular medicine? Can't the argument be made that the shotgun approach is much less expensive than pursuing the goals of the MMG?

Yet, if we accept the shotgun approach of the CICI, it seems an admission that the guiding biological paradigms of the past 50 years are either dead or seriously wounded. On the brighter side, the shotgun approach would seem to bolster the growing argument for a dimensional approach to psychiatric diagnoses, rather than the present classical categorical system. As of 2010, however, psychopharmacology and psychiatry have been, with few exceptions (Healy, 1977; Moncrieff and Cohen, 2005) unwilling to confront the question of non-specificity, or even to recognize the paradoxical goals of the MMG and CICI. For example, the newest editions of two prominent textbooks (The American psychiatric publishing textbook of psychiatry, 2008; Neurobiology of mental illness, 2009) have nothing on the subject. They fail to even mention the possibility that some psychotropics may be acting in non-specific ways, thus yielding improvement in multiple disorders. The other, no doubt equally unwelcome possibility, is that the proposed pathogenesis of many disorders is simply way off the mark—or perhaps too complex to be understood.

Further complicating matters is the contamination of the scientific literature by a host of players, including Big Pharma (Angell, 2004), which has hidden negative studies (Turner et al., 2008), hired nationally-known investigators as lead authors on papers authored primarily by company ghost writers (Ross et al., 2008), spent about $1 billion yearly on continuing medical education (Wilson, 2010a), changed primary outcome measures when results were less than expected—but without acknowledgment (Vedula et al., 2009), and mounted an enormous effort aimed at marketing drugs for off-label purposes, despite, in some instances, repeatedly paying fines exceeding one billion dollars for violating FDA standards (Singer, 2009). But we can't place the blame for the deterioration in the literature only on the pharmaceutical industry: universities and their faculty members have been complicit in these practices, even permitting faculty to sit on the boards of directors of Pfizer, Merck, and other companies (Wilson, 2010b), while internationally-known faculty members are alleged to have hidden income from the drug industry, sometimes amounting to over $1 million (Angell, 2009). In addition, journal editors were slow to recognize the ethical and scientific implications of the takeover of psychiatric research by industry. Similarly, NIMH turned its back on comparative studies of FDA-approved agents (Klein, 2008), leaving clinical investigators desperate for funding.

2. Depression and antipsychotics: a paradox?

We have already mentioned the growing number of APs now FDA-approved for the treatment of depression, including aripiprazole as adjunctive therapy for major depression and quetiapine as monotherapy for bipolar depression. What is the neurochemical basis for this development? I have chosen this particular issue in part because of the seemingly rather stark contrasts between the mechanisms by which APs and ADs appear to work, in part because of the ubiquity of depression and the large number of treatment-resistant cases, and in part because of the potentially enormous costs of routinely treating depression with both ADs and APs, not to speak of the costs of dealing with the metabolic consequences of the long-term use of APs in this population.

A recent review (Bogart and Chavez, 2009) of the efficacy and safety of quetiapine documented its efficacy in 5 RCTs and several subanalyses. The authors stated that the antidepressant mechanism of action of quetiapine is unknown, although they hypothesized that the pathophysiology of bipolar depression might be different from that of major depression. However, the authors provided no data to back the assertion of a basic difference between bipolar and non-bipolar depression, nor did they propose any pathophysiologic basis for the antidepressant effect of quetiapine. Similarly, a meta-analysis (Nelson and Papakostos, 2009) of controlled trials of atypical antipsychotic augmentation in major depression found a significant advantage over placebo (OR = 1.69, 95% CI = 1.46–1.95), but no discussion of the pathophysiology. Those who have discussed the pharmacological basis for this development (Ostroff and Nelson, 1999; Berman et al., 2007; McIntyre et al., 2007) have focused on two primary factors: blockade of 5-HT2 receptors, and the partial agonist activity of aripiprazole at 5-HT1a, DA2, and D3 receptors.

3. The monoaminergic paradox

Assuming that some APs are indeed efficacious for depression—whether as monotherapy or as adjunctive agents—is this not a paradox? Here is a fundamental, albeit simplified question: how do we reconcile the anti-dopaminergic effects of APs and the pro-dopaminergic effects of ADs? Is it not the case that APs are thought to exert their primary effects by blocking dopamine receptors (with varying degrees of affinities for the 5 DA receptor subtypes), such that a blockade of D2 receptors (D2Rs) is common to all currently marketed APs?

It is the case, however, that while D2R blockade may be necessary for an AP effect, it is not sufficient, since PET and SPECT studies have shown an equal degree of blockade in responders and non-responders (Wolkin et al., 1989; Pilowsky et al., 1992). Of interest, another study (Wolkin et al., 1994) of treatment-resistant patients with schizophrenia given alpha-methyl paratyrosine in conjunction with APS, found a 72% decrease in plasma HVA, but no change in the severity of psychotic symptoms. In a detailed review (Talbot and Laruelle, 2002) of striatal D2R rates of occupancy by risperidone, clozapine, and olanzapine, rates varied from 16 to 89%. Another problem is the up-regulation of D2Rs by APs, although individual agents vary considerably in their effects (Silvestri et al, 2000), since the up-regulation of D2Rs has been associated with treatment failure, despite high levels of D2 occupancy (Samaha et al., 2007). Kapur and Seeman (2001) have suggested that another factor, namely rapid dissociation from the D2R, is the most important process in the mode of action of atypical APs. In addition, blockade of certain serotonin receptor subtypes is common to atypical agents, but these authors doubt that this action is either necessary or sufficient to explain atypicality.

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We should therefore acknowledge other hypotheses regarding modes of action of APs, including up-regulation of immediate early genes (IEGs) in the forebrain, Papez circuit and thalamus (Robertson and Fiberger, 1992; Cochran et al., 2002), agonistic effects by novel agents at mGlu2/3receptors (Patil et al., 2007) although the authors note that this pathway may have an anti-dopaminergic effect, and cholinergic agonists (Lieberman et al., 2008a), since several investigators have found that atypical APs increase levels of acetylcholine in the prefrontal cortex of rats. However, there are significant interactions between acetylcholine and dopamine, which in some instances result in antagonism of D2Rs. There is also a growing interest in the neuroprotective effects of APs (Lieberman et al., 2008b), a topic we shall explore later.

Despite the emphasis on various non-dopaminergic hypotheses, and the problem of similar occupancy of D2 receptors in responsive vs non-responsive patients, most would agree that some degree of DA receptor blockade appears to be important for an AP effect, *yet dopaminergic hypofunction may be important in the pathogenesis of depression*. Gershon et al. (2007) have provided an overview of the evidence for decreased DA transmission in depression, as well as evidence that chronic AD use increases D2R binding and D3R mRNA in the nucleus accumbens (nAc). In addition, they note the AD effects of DA agonists, and the possibility that activation of the cyclic-AMP response-element-binding protein (CREB)–BDNF pathway may lead to DA supersensitivity in the nAc. Others, however, have not found an increase in D2R density, but rather a significant increase in mRNA coding for D2Rs in rat caudate-putamen with chronic (14 days) use of imipramine (Dziedzicka-Wasylewska and Rogoz, 1998). Interestingly, fluoxetine given for 8 weeks to rats significantly increased D1 and D2 receptors in the nAc and olfactory tubercle (Hammer et al., 1993). Similarly, repeated administration of tricyclic ADs results in DA autoreceptor subsensitivity, whereas haloperidol results in DA autoreceptor supersensitivity (Choido and Antelman, 1980).

In general, it appears that ADs have dopaminergic effects, which is consistent with the simplified hypothesis of dopaminergic hypofunction in depression. Yet in virtually all such studies the authors emphasize that these receptor changes require chronic administration of ADs, and that the time delay correlates with the time to clinical response. This argument, well-established in the research literature as well as in major textbooks (Martinez et al., 2008, p.1057; Duman, 2009.p.414) is becoming outmoded, given several meta-analyses which have shown a measurable AD effect within the first 1–2 weeks of administration (Posternak and Zimmerman, 2005; Taylor et al., 2006; Papakostas et al., 2006).

From another perspective, there are a number of mechanisms by which ADs seem to work. To what extent are these processes duplicated by APs? I will use the discussion by Duman (2009) as a guide, since he has provided an overview of both preclinical research and its application to ADs generally.

4. Monoamines

We have already pointed out the monamine paradox, although Duman (2009) does not address this issue with regard to the antidepressant effects of APs. He notes, as do most investigators, that a simple focus on monamines is not sufficient to explain AD effects, with the primary argument being the disconnect between the rapid increase in monamine turnover and the alleged delay in clinical response. This argument was made by Charney et al. (1981) who cited evidence that a time delay was necessary for adaptive changes in receptor functioning.

As I just mentioned, this argument has been pervasive in both the clinical and basic science literature to the present day, despite evidence to the contrary. Given the persistence of this argument, however, the effect of APs on these receptors is worth examining. The commonly cited AD-induced changes include a reduction of firing of autoinhibitory monamine neurons, down-regulation of β adrenergic receptors (βARs) and 5-HT2a receptors by some ADS, and an increase in 5-HT1a receptor transmission.

While Duman (2009a) has stated that the down-regulation of βARs is not important for an AD response, the question remains open. In any event, APs have little or no effect on βARs, whether they be atypicals or conventional (Bymaster et al., 1996). In a similar vein, some, but not all ADs bind to 5-HT2a receptors when used chronically. Todd et al. (1995), for example, found that administration of clomipramine, fluoxetine, phenelzine, and maprotiline over a 21-day period decreased binding to 5-HT2a receptors in the rat brain. Desensitization of 5-HT2a receptor function occurs with chronic administration (Yamauchi et al., 2006). With regard to the 5-HT2c receptor, fluoxetine, norfluoxetine, and citalopram bind to this receptor with relatively high degrees of affinity (Palvimaki et al., 1996).

Blockade of various 5-HT receptors by atypical APs is common. Multiple atypical APs bind with high degrees of affinity (Bymaster et al., 1996) to 5-HT2a, 2c, and 5-HT3 receptors, with Ki(nM)s ranging from 0.6 ± 0.2 (risperidone, at 5-HT2a) to 4 ± 0.4 (olanzapine, at 5-HT2a). Yet quetiapine, despite its growing role in the treatment of depression, is considerably less potent (Bymaster et al., 1996), with affinity constants for 5-HT receptors that are much lower (5-HT2a, 220 ± 4; 5-HT2c, 615 ± 110; 5-HT3, 170 ± 15). Aripiprazole, in contrast to quetiapine, is a potent 5-HT2a and 1a blocker (5–30 nM), but is less potent at 5-HT2c (Stark et al., 2007). As is well-known, aripiprazole is also a partial agonist at 5-HT2a and 5-HT2c receptors and both D3 and D4 receptors (Shapiro et al., 2003).

It appears, then, that at least *some ADs and APs have in common the ability to bind and down-regulate 5-HT2a and 2c receptors*, but is this process critical for an antidepressant effect? The answer appears to be mixed at best, since 5-HT2a receptor antagonists given alone are not effective, not all ADs down-regulate 5-HT2a receptors, and electroconvulsive therapy increases 5-HT2a receptor density (Duman, 2009). A positive argument comes from the apparent effectiveness of some atypical APs as augmenting agents—but this is a clinical observation, and does not address the underlying neurochemistry.

With regard to 5-HT1a receptor sensitivity, it is important to stress that presynaptic 5-HT1a receptors are autoinhibitory and help regulate 5-HT neurons projecting to the forebrain (Artigas et al., 1996). While post-synaptic 5-HT1a receptors are found in the limbic and cortical areas, the dorsal raphe nuclei have a high density of presynaptic 5-HT1a autoreceptors and 5-HT uptake sites. Desensitization of 5-HT1a autoreceptors by some ADs given chronically results in increased firing rates of 5-HT neurons in projection areas (Artigas et al., 1996). Several studies (Artigas et al., 1996) have shown that pindolol, a 5-HT1a antagonist, can speed the response to serotonergic reuptake inhibitors (SSRIs), apparently by blocking the *acute* SSRI-induced increase in 5-HT in the midbrain raphe nuclei, an increase which activates the 5-HT1a autoreceptor.

The effects of APs on 5-HT1a receptors differ considerably from ADs, since most APs act as agonists at these receptors. For example, ziprasidone, clozapine, and olanzapine *activate* 5-HT1a receptors, and in a dose-dependent fashion *decrease* the firing rate of serotonin neurons in the dorsal raphe nuclei (Sprouse et al., 1999). Other work has shown that the activating effect of clozapine on 5-HT1a receptors in the rat prefrontal cortex is associated with an *increase* in DA release in that area (Rollema et al., 1997), with similar results found for olanzapine and ziprasidone, but not haloperidol (Diaz-Mataix et al., 2005). The increase in prefrontal DA associated with 5-HT1a activation is interesting, and no doubt results from the fundamental fact that 5-HT is a DA inhibitor, such that the autoinhibitory effect of an agonist at this receptor results in a decreased release of 5-HT and an increase in DA. This process might contribute to an antidepressant effect of some APs, but it is clear that the primary effects of ADs and APs differ markedly at this receptor. Interestingly, the action of ADs at

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5-HT1a would seem to argue against a pro-DA effect, although this might be overridden by the other processes described by Gershon et al. (2007).

5. The 5-HT transporter (5-HTT) and antipsychotics

A fundamental process in the mode of action of SSRIs is the binding of SSRIs to 5-HTT, thus preventing the transport of 5-HT into presynaptic neurons, and thereby increasing availability of 5-HT at the synapse. Whether genetic variation at the SLC6A4 locus influences the response to SSRIs has been the subject of intense research, albeit with mixed results, and, in one recent study of a very large sample examining multiple SNPs, shows clearly negative results (Kraft et al., 2007). Our issue, however, is whether APs have any significant interaction with the 5-HTT. One group (Stark et al., 2007) reported that aripiprazole, has low affinity for 5-HTT (Ki = 98 nM). Tatsumi et al. (1999) investigated the equilibrium constants ($K_D \pm$ S.E.M.) of 37 APs for 5-HTT, the DA and NE transporters (DAT and NET), and found that only chlorpromazine and ziprasidone had significant potency at 5-HTT, although the metabolite of quetiapine, N-desalkyl quetiapine, does inhibit the NET, with a Ki of 12 nM (Jensen et al., 2008).

Interestingly, in view of recent work emphasizing the usefulness of atypical APs in depression, it appears that these agents are quite weak at the 5-HTT (Tatsumi et al., 1999). For reference, the $K_D \pm$ S.E.M. of paroxetine was 0.13 ± 0.01, whereas for risperidone and quetiapine it was >10,000, for olanzapine 1310 ± 40, and for clozapine, 1330 ± 50. Others (Tarazi et al., 2000) have found that quetiapine, olanzapine, and risperidone failed to alter tissue levels of 5-HTT in various subregions of the rat striatum.

It seems unlikely, then, that atypical APs significantly block the reuptake of 5-HT. Interestingly enough, serotonergic antagonism by atypical antipsychotics is at the core of a model of hyper-serotonergic function in schizophrenia proposed by Scarr et al. (2001). Indeed, this group felt that serotonergic antagonism common to atypical APs may be responsible for the "increased clinical effectiveness" of these agents, a statement commonly found in such research, but one which appears to be incorrect, given recent meta-analytic studies showing little difference in efficacy between conventional and atypical agents (Geddes et al., 2000; Rosenheck et al., 2003; Lieberman et al., 2005; Jones et al., 2006). For our purposes, however, we have to emphasize that *if atypical APs have significant antiserotonergic effects, this would seem to run counter to the neurochemical effects of SSRIs.*

6. Neuroprotective effects of antidepressants

Given the problems associated with the focus on monoamines in the pathophysiology of depression and as an explanatory construct in the mode of action of ADs, investigators have increasingly turned to their effects on neuroprotection, neurogenesis, and synaptic connectivity in a lengthy review of molecular and cellular mechanisms in depression, Duman et al. (1997) drew attention to the increase in the expression of neuroprotective proteins with the chronic use of ADs, noting that levels of brain-derived neurotrophic factor (BDNF)mRNA as well as levels of CREB protein were increased in the hippocampus. The interaction between and among depression, stress, changes in hippocampal volume and neurotrophins became a focus of interest, but the enthusiasm has been tempered somewhat by work showing that sleep disruption, exercise, and inflammatory processes all have a hand in regulating neurogenesis and levels of neuroprotective proteins (Lucassen et al., 2010). Others (Sairanen et al., 2007) have shown that ADs have shown positive effects on synaptic plasticity, with Altar (1999) finding that both BDNF and neurotrophin-3 (NT-3) stimulate the regrowth of 5-HT neurons in the brains of adult rats, and that the AD-induced increase in BDNF seems to work via effects on 5-HT2a and βARs. Indeed, Mattson et al. (2004) have emphasized the interaction of 5-HT and BDNF, with BDNF enhancing the growth of 5-HT neurons, while 5-HT increases the expression of BDNF.

However, as Balu et al. (2008) have reviewed, some have found no increases in BDNF mRNA after chronic treatment with either tricyclic ADs or SSRIs. Moreover, others (Krishnan and Nestler, 2008) have reviewed additional problems with the BNDF hypothesis, noting for example, that stress and antidepressants have shown decreases in BNDF, that male mice with conditional knockouts of BDNF or its receptor fail to develop behaviors consistent with depression, and that regional effects are important, since infusion of BDNF into the ventral tegmentum and nAC *induces* depressive behaviors.

7. Do antipsychotics have neuroprotective effects?

Despite the negative studies, it seems fair to say that research on neuroprotection has come to occupy a central role in the study of the pathophysiology of depression and the mode of action of ADS (Duman, 2009). That being the case, we must ask if APs have similar effects. In a typical study, Balu et al. (2008) examined the effects of several ADs (desipramine and fluoxetine) and APs (haloperidol and clozapine) given acutely or chronically on levels of BDNF in regions of the rat brain, and found that a 3-week course of ADs increased levels in the frontal cortex by 10–30%, but had no effect in the hippocampus, brain stem, olfactory bulb, or amygdala. Similarly, a 3-week course of haloperidol or clozapine led to an 8–10% increase in the frontal cortex, although haloperidol also increased BDNF levels in the amygdala, while clozapine led to a decrease in the olfactory bulb. Interestingly, a 10-day course of electroconvulsive stimuli (ECS) led to a 100% increase of BDNF in the hippocampus and amygdala and a 40% increase in the frontal cortex and brain stem, but no change in the olfactory bulb.

As in most studies, the authors emphasized that acute treatment had no effect, regardless of the drug. However, the time frame was not remotely similar to any clinical application, since "acute" was defined as *one day* of drug administration or one application of ECS (which did result in a 25% decrease of BDNF in the amygdala). Since the studies cited earlier have shown that ADs may lead to a clinical response within 7–14 days, it would have been interesting to have had another sample wherein ADs and APs were given for at least 7 days.

Lieberman et al. (2008b) have provided a detailed review of the many studies examining the effects of both typical and atypical APs on neuroprotection in various areas of the brain, and concluded that there are differential effects of these agents on BDNF, NGF, and cell proliferation. In contrast to the effects of ADs, levels of NGF in rat hippocampus *declined* to levels below that of control groups, although the decrease was less with atypical APs than conventional agents. However, this was dependent on the brain area, with levels of striatal BDNF and NGF being markedly *reduced* by all APS. In other studies, atypical APs had little or no effect on neurotrophic factors, whether given for 3 days or 21 days. On the other hand, NGF and BDNF levels in the rat striatum, sensory motor cortex, and hippocampus significantly increased after 7–14 days whether given haloperidol, olanzapine, or risperidone. In Table 2 of their article, 34 studies are cited, with only 4 showing an increase in levels of BDNF or NGF, while 24 found a decrease. The decrease in neurotrophins appears to be a consequence of the D2R blocking effect of APs. Yet other investigators (Valvassori et al., 2008) have found that chronic treatment with antipsychotics simply had no effect on levels of BDNF or NGF in the rat hippocampus, despite daily injections of haloperidol, clozapine, olanzapine, or aripiprazole.

As Lieberman et al. (2008b) have pointed out, these studies were marked by a number of problems, including the dominant use of haloperidol as a comparison agent, and the use of rodents as the experimental animal. In the few studies of humans involving the measurement of neurotrophins and their response to APs, the results have been mixed, with most showing *reductions* in NGF with AP

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treatment. These findings do not seem consistent with the generally positive effects of ADs on neurotrophins, and thus provide little evidence to support a neurotrophic effect of APs as a foundation for their antidepressant effects.

However, there may be instances wherein a reduction in BDNF could be therapeutic, since in the case of mice subjected to social defeat stress, BDNF levels in the nAc are increased, with the gene effects reversed by ADs (Berton et al., 2006). As with ADs, investigators have frequently emphasized the chronic vs acute effects of APs, but, as we have seen with ADs, recent studies have found that a significant antipsychotic effect occurs in the first 2 weeks of treatment (Agid et al., 2006; Leucht et al., 2005).

8. Antidepressant-induced cell proliferation and neurogenesis

Perera et al. (2007) have reviewed the evidence for induction of neurogenesis in the hippocampus by ADs and electroconvulsive stimuli (ECS), a process which according to the classic study of Santarelli et al. (2003) is necessary for the antidepressant-induced behavioral changes found in mice treated chronically with either noradrenergic or serotonergic agents. Since these studies were done principally in rodents, Perera et al. (2007) studied the effects of ECS in adult monkeys (male bonnets), and found a robust increase in precursor cell proliferation compared with sham ECS and untreated controls, as well as a significant increase in BCL2, a neuroprotective gene product, immediately after treatment and at 4 weeks post-treatment. The increase in cell proliferation was not a result of cell death secondary to ECS. At 4 weeks, the majority of precursor cells had differentiated into mature neurons and endothelial cells, although the percentages of precursor cells that matured were similar in treated and untreated animals. The authors noted that ADs and ECS also induced precursor cell stimulation in rodents, but did not alter rates of maturation, a process likely to be controlled by BDNF or other nerve growth factors.

Although the authors suggest that convulsive therapy in humans may result in a similar outcome, they caution that the role of the ECS-generated neurons is not known, and indeed that AD-induced neurogenesis may be an epiphenomenon, particularly since other studies have found no reduction in hippocampal precursor cells in post-mortem human studies of depression (Reif et al., 2006), or in learned helplessness in rats (Vollmayr et al., 2003). Similar arguments were made by Henn and Vollmayr (2004), who found no evidence that a decrease in neurogenesis results in depressive behaviors.

9. Do antipsychotics induce neurogenesis?

A number of studies have found that APs induce neurogenesis (see Lieberman et al., 2008b for a review) in the subventricular and subgranular zones of the rat hippocampus, with more consistent results secondary to chronic administration of atypicals, and, in some cases, no increase in proliferation or increased survival time with haloperidol. With regard to the contrast between atypical and conventional APs, the authors cited a study by Halim et al. (2004) in which haloperidol failed to increase neurogenesis or survival in the hippocampal dentate gyrus, but the authors (Lieberman et al., 2008b) failed to add that low dose clozapine, while doubling the number of new cells at 28 days, had no effect at either low or high dose after an additional 3 weeks.

With regard to the recent FDA approval of atypical APs for depression, some have proposed an additive effect of combined treatment with AD and AP on BDNF expression and hippocampal neurogenesis (Xu et al., 2006). These investigators therefore administered quetiapine, venlafaxine, or the combination to rats for 3 weeks, then, during the last 2 weeks, subjected the rats to chronic restraint stress (CRS). As expected, CRS decreased both BDNF and cell proliferation in the hippocampus, but the combination of low dose quetiapine and low dose venlafaxine not only blocked the decrease in BDNF but increased cell proliferation, whereas the same low dose of the drugs given separately had only a mild effect. However, when the dose was doubled (10 mg/kg of quetiapine and 5 mg/kg of venlafaxine), each drug given separately had effects comparable to the combination. It seems reasonable to conclude that this is a dose-dependent effect of each drug, and that from a clinical and cost perspective, simply giving a higher dose of one agent would be preferable.

10. Neurotrophins, neuroprotection, and neurogenesis with antidepressants and antipsychotics: clinically relevant?

While there is some evidence that ADs and APs confer a degree of neuroprotection and also induce neurogenesis, the question is whether these processes have any significant clinical relevance, and, if so, whether they account for the antidepressant effect of APs. A number of issues seem important in such a discussion.

First, much of the work in this area is based on studies in rodents subjected to various forms of laboratory stress, procedures which bear little resemblance to common stressful experiences in humans. One dislikes stating the obvious, but a rodent in tube restraint is hardly a model for an adult living in poverty, facing chronic unemployment, divorce, the development of a life-threatening malignancy, or combat in Afghanistan. There are also questions regarding epigenetic influences (Tsankova et al., 2007), species differences, and in rodents, differences in response to AD treatment among different strains, with further modification depending on age and the laboratory environment (Pollak et al., 2010). Not surprisingly, several investigators have emphasized the lack of consistency in treatment effects when animal experiments are compared with clinical trials in humans (Perel et al., 2007).

Second, the induction of neurogenesis is not limited to ADs and APs (Perera et al., 2007), but can be induced by mood stabilizers, environmental enrichment, and chemically or electrically-induced seizures. Even moderate exercise can have a significant effect, as shown by Pajonk et al. (2010), who found a 12–16% increase in hippocampal volume in both male patients with chronic schizophrenia and matched controls. Similarly, aerobic fitness has been found to correlate positively with hippocampal volume (Erickson et al., 2009). Therefore any investigation of AP or AD-induced neurogenesis must take into account prior drug treatment, history of ECT, and the activity level of the subjects, but these potential confounds often are not addressed.

Third, a theme common to both animal and human studies is the emphasis on the differential effects of classes of ADs (SSRIs vs TCAs) and APs (conventionals vs atypical) on neurotrophins and neurogenesis. In the case of APs, this is quite explicit in Lieberman et al. (2008b) who noted on p. 375 of their paper a list of the various observations supporting the proposed "clinical superiority" of atypicals. They concluded that atypicals may limit neurodegeneration and act as neuroprotectants, but even if this finding is consistent, does it matter clinically? We have previously cited the many studies that have shown little difference in efficacy between conventionals and atypicals, although the latter may differ in limiting extra-pyramidal side-effects, although some studies have failed to show a significant advantage in that area as well (Lieberman et al., 2005; Jones et al., 2006). A reasonable conclusion is that atypicals may offer some advantage in stimulating neuroprotective processes but there is little evidence that this affects outcome. In an earlier review (Dean, 2006), this author noted a similar disjunction between and among antipsychotic-induced neuronal changes, symptoms, and outcome in schizophrenia.

With regard to ADs, the evidence is even clearer that SSRIs have shown no gain in efficacy over TCAs (Andersen and Tomensen, 1994; Song et al., 1998), although they are safer in overdose and appear better tolerated. In addition, the efficacy of ADs generally has been

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called into question with some proposing that at best they yield a two point improvement in rating scales (Kirsh et al., 2002) and may be no better than placebo in mild to moderate depression (Kirsch et al., 2008; Fournier et al., 2010). Once again we find a disjunction between findings in the laboratory and clinical outcome studies, a gap which needs more recognition, particularly by bench scientists.

11. Antipsychotics, antidepressants, and epigenetics

An important issue in both the etiology and treatment of psychiatric disorders is the persistence of symptoms over long periods of time, leading some to propose that epigenetic regulation of gene expression might be one molecular mechanism underlying the persistence of maladaptive as well as adaptive brain changes (Tsankova et al., 2007). Although these authors have continued to emphasize the debatable conclusion that long-term treatment with psychotropic agents is necessary for their therapeutic effects, if epigenetic changes contribute to symptom persistence, it follows that APs and ADs might function—at least in part—by reversing or mitigating harmful epigenetic changes via modification of chromatin structure (Sharma, 2005).

Briefly, epigenetic changes can occur in a number of ways (Tsankova et al., 2007), including remodeling of chromatin via acetylation or methylation at the histone 2A, 2B, H3, and H4 N-terminal tails, as well as phosphorylation of amino acid residues. Acetylation is catalyzed by histone acetyltransferases, and generally increases gene activity, but this can be reversed by histone deacetylases (HDACs), which in many cases suppress chromatin activity. Phosphorylation can result in either increased or decreased gene activity. Overall, the level of gene activity appears to be closely associated with cycling between acetylation and deacetylation. Methylation, in which a methyl group is transferred from S-adenosyl methionine to cytosine residues or from cortical DNA-methyltransferase 1 (Veldic et al., 2005) in GABAnergic interneurons can be either repressive or activating. Other, but less well-known mechanisms, include nucleosome sliding, SWI/SNF, a protein complex involved in the mediation of nucleosome sliding, and SUMOylation.

12. Antipsychotics and epigenetics

A number of investigators have found evidence of epigenetic dysfunction in schizophrenia (see Rutten and Mill, 2009 for a review), including differences in methylation of cytosine pyrimidine (CpG) sites in genes for the D2 receptor and COMT, and increased levels of DNA-methyltransferase-1 (DNMT-1) which have been associated with changes in the glutamic acid decarboxylase67 (GAD67) promoter and down-regulation of reelin (Reln) transcription (Dong et al., 2005). Indeed, down-regulation of reelin has been found in brains of patients with schizophrenia. Since reelin is found in GABA neurons, and GAD67 is decreased in cortical interneurons (Veldic et al., 2005), some have proposed that the end result is compromised function of GABAnergic neuronal networks, and disruption of higher-order neuronal networks (Tsankova et al., 2007).

Can antipsychotics modify or reverse hypermethylation? A few investigators have found a direct effect of some atypical APs on this process. For example, Dong et al. (2008), have shown that clozapine and sulpiride significantly increased demethylation in the cortex and striatum of mice that had been pretreated with a methyl donor aimed at increasing methylation of GAD67 and reelin. However, haloperidol and olanzapine had no effect. Moreover, valproate, a known HDAC inhibitor, markedly potentiated the effects of clozapine and supiride. Others (Guidotti et al., 2007) have reported that the cumulative dose of fluphenazine did not lower the significantly elevated levels of the methyl donor S-adenosyl methionine and DNMT-1 mRNA in patients with schizophrenia and bipolar disorder. We should also note that neither the time of onset or duration of the illness had no relationship to levels of either molecule, which seems surprising in view of the putative role of epigenetic influences on chronicity.

With regard to the role of valproate, this was investigated by Veldic et al. (2005), who studied tissue levels of GAD67 and DNMT-1 from Brodmann's area 9 in psychotic patients with schizophrenia and bipolar disorder. They found an increase in cortical DNMT-1 with a parallel decrease in GAD67-expressing neurons in schizophrenia, but not in bipolar patients who were not psychotic. In those patients with schizophrenia and psychotic bipolar disorder treated with a combination of AP and valproic acid, the increase in DNMT-1 was not statistically significant. The presence, absence, or dose of APs had no effect on either parameter, but only 2 patients had never been given APs; another 7 had been medication-free for 3 months prior to death. A history of substance abuse/dependence had no effect on the findings, and, in contrast to Dong et al. (2008), the type of AP had no differential effect. Given the co-morbidity of both conditions with major depression, it seems odd that in Table 4 (p.2153) of their paper, there was no mention of prior AD treatment or electroconvulsive therapy.

Veldic et al. (2005) concluded that the increased expression of DNMT-1 is not due to AP treatment, nor does AP treatment prevent DNMT-1 up-regulation, although the combination of AP and valproate may lessen the increase; however, they recommended that other and perhaps more effective HDAC inhibitors be studied. Finally, they suggested that the increase in DNMT-1 is important to the down-regulation of GAD67 and reelin.

Despite the lack of AP effect on up-regulation of DNMT-1, there are other pathways by which APs might affect chromatin remodeling, including acetylation of histone A4 and phosphoacetylation of histone A3 in rat striatum, leading to increased transcription of c-fos (Li et al., 2004). In addition, haloperidol and raclopride have been shown to induce histone H3 phosphorylation in the dorsal striatum of mice, but with no change in acetylation (Bertran-Gonzalez et al., 2009). It appears that H3 phosphorylation is increased by D2 receptor blockade, but opposed by adenosine A2A receptors. Others (Dong et al., 2008) have found that histone H3 hypermethylation can induce demethylation of both reelin and GAD67.

Although some APs have been shown to accelerate demethylation and increase immediate early gene activity, and thus function as HDAC inhibitors, it is also the case that cocaine and seizures can induce H4 acetylation and H3 phosphoacetylation, with activation of c-fos (see Tsankova et al., 2007, for a review). Levels of maternal nurturing can also increase DNA methylation, an effect which lasted into adulthood, but could be reversed either by cross-fostering or an HDAC inhibitor (Weaver et al. 2004).

What can we conclude from this brief survey? It appears that some APs can indeed have an impact on the epigenome via several pathways, including demethylation, phosphorylation of histone H3, and acetylation of histone H4. However, it is not at all clear whether atypicals have any obvious advantages over conventional agents in this regard, and indeed whether atypicals as a group have such effects. Although the effects of valproate in combination with APs are quite interesting, whether APs alone have a significant impact on clinical outcome via epigenetic changes has yet to be demonstrated. In addition, separating out drug effects from changes in the environment appears to be challenging, not to speak of clarifying the epigenetic effects of polypharmacy.

13. Antidepressants and epigenetics

We earlier reviewed the issues surrounding the recent emphasis on a deficiency of BDNF in the pathogenesis of depression, a hypothesis which is linked to epigenetic factors in depression.

Martinowich et al. (2007) have emphasized the very complicated genome of BDNF, noting the presence of at least 4 promoters which are both differentially distributed and differentially activated by stress

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and other signaling events. Chronic social defeat stress (SDS) in mice leads to persistent down-regulation of BNDF splice variants III and IV in the hippocampus but this can be reversed by chronic treatment with ADs. BNDF promoter III is particularly relevant to this discussion, since its transcription is suppressed by MeCP2, a suppressor that binds methylated DNA, and acts in conjunction with HDAC1 and Sin3a, another suppressor.

However, chronic SDS also induces a significant and persistent increase in dimethylation (addition of 2 methyl groups) at H3, which also suppresses chromatin functioning and decreases BDNF transcription. Interestingly, treatment with imipramine or chronic ECS can counter the suppression of the BDNF transcripts by increasing acetylation of H3 and decreasing levels of HDAC5 in the hippocampus (Tsankova et al., 2006). However, the authors note that matters are not so straightforward, since the BDNF precursor, proBDNF, appears to induce anxiety states, and BDNF itself can have opposing effects, with induction of depression when active in the ventral tegmentum–nucleus accumbens reward system.

Yet another positive neuronal adaptation in mice subjected to SDS (Covington et al., 2009) involves a persistent increase in H3 acetylation and a decrease in HDAC2 in the nucleus accumbens, with similar changes found in the nAC of depressed humans. The authors note that these changes have normalizing effects on stress-regulated genes, with "striking similarities" to those found after administration of fluoxetine. However, since the chronic administration of fluoxetine *does not result in an increased level of H3 acetylation or lower levels of HDAC2 in the mouse nAC*, it would seem that HDAC inhibition, via administration of HDAC inhibitors, could represent a unique approach to the treatment of depression.

With regard to our concerns regarding specificity, such an approach at this point appears to be non-specific, since current HDAC inhibitors are broad-spectrum (Abel and Zukin, 2008). Indeed, the authors note that in the many neurodegenerative and psychiatric disorders under review, none have been associated with a specific HDAD. However, they also note that cognitive deficits are common to all these disorders, including schizophrenia, depression, Huntington's disease, Parkinson's disease, Alzheimer's disease, and others, and that reduced histone acetylation is common to all.

14. Acid-sensing ion channels and depression

Another newer approach to the treatment of depression and the mechanisms of AD action has been the recent focus on acid-sensing ion channels (ASICs). These are a subgroup of the degenerin/epithelial Na + family of cation channels (Wemmie et al., 2006) that are gated by extracellular protons and encoded by 3 genes with alternatively spliced transcripts, ASIC1a, 1b, 2a, 2b, and 3. They appear to have multiple functions, including modulation of pain, synaptic plasticity, and memory, as well as involvement in the pathophysiology of stroke. However, there are a number of fundamental questions about their roles in all of these areas (Wemmie et al., 2006).

Nevertheless, since ASIC1a is found in the amygdala, the nucleus accumbens and other structures associated with depression, and, since hyperactivity of the amygdala has been found in patients with major depression (Drevets et al., 1992), Coryell et al. (2009) undertook an investigation of the effects of ASIC1a in rodent models of depression, including the forced swim test and the tail-suspension test. Inhibition or loss of ASIC1a (whether induced genetically or with inhibitors) produced robust antidepressant-like effects which were not dependent on serotonin depletion, nor did the antidepressant effects of monamine reuptake inhibitors require ASIC1a. Interestingly, disruption of this channel did not affect the corticosterone response to stress, but ASIC1A mice under stress did not have lower levels of BDNF, indicating a corticosterone-independent pathway in BNDF regulation. The authors also found that viral vectors which restored ASIC1a expression in the basolateral amygdala of ASIC1a null mice led to an increase in immobility in the force swim and tail-suspension tests, thus supporting previous work indicating that the amygdala is a key site in the regulation of mood.

As with HDAC inhibitors, Coryell et al. (2009) have suggested that ASIC1a inhibitors might point to a novel and obviously quite different pathway to the treatment of depression. The inhibitors used in this study, however, include tarantula venom and an amiloride-like compound, but whether either of these have any potential in humans is not clear. The possible impact of APs on ASIC1a on the treatment of depression remains unknown.

15. Antipsychotics, antidepressants, and sigma receptors

In recent years attention has turned to the interplay of antidepressants, antipsychotics, and sigma receptors 1 and 2. These receptors were originally classified as opioid receptors, but are now classified as non-opioid receptors, with a focus on the sigma-1 receptor which is found primarily in the endoplasmic reticulum of neurons and oligodendrocytes in the hypothalamus, olfactory bulb, the deep laminae of the cortex, and brain Purkinje cells. They are also found in the hippocampus and substantia nigra (see Dhir and Kulkarni, 2007 for a review). Sigma-1 receptors appear to be involved in learning, memory, drug dependence, cellular differentiation, membrane remodeling, release of dopamine and serotonin (Bermack and Debonnel, 2005), and regulation of glutamate NMDA receptor functioning (Hayashi and Su, 2004; Hayashi and Su, 2005). Lee et al. (2008, p.124)) have stressed that the wide distribution of these receptors, and their "unparalled ability to interact with a huge range of drug structural classes" have resulted in their being proposed as targets for multiple disorders ranging from Alzheimer's disease to stroke.

A number of studies now suggest that sigma-1 receptors may be involved in the pathogenesis of depression. Sigma-1 knockout mice display increased immobility in the forced swimming test, a classic rodent model of depression, but have normal locomotor activity (Sabino et al., 2009), while sigma-1 agonists such as igmesine have antidepressant effects in animal models, mediated by modulation of Ca (2+) release and neuritogenesis (Takebayashi et al., 2004). Others (Wang et al., 2007) have found that a sigma-1 antagonist reduced the antidepressant effects of sigma-1 agonists.

Some years ago Reddy et al. (1998) found that the antidepressant effects of neurosteroids were mediated by the sigma receptor. This group of investigators (Dhir and Kulkarni, 2007) then found that a high affinity sigma-1 receptor agonist, (+)-pentazocine, given prior to treatment with a subeffective dose of venlafaxine, produced a synergistic effect in the mouse forced swim test. On the other hand, several sigma-1 antagonists (progesterone, rimcazole, and BD 1047) reversed the anti-immobility effects of venlafaxine, which had been found to occur in a dose-dependent fashion.

While this study is interesting and informative, we should note that a single dose of venlafaxine was given 30 min prior to the forced swim test, and the agonists/antagonists were given 15 min prior to the venlafaxine. Thus, we have no data on how time or repeated administration of the same dose might affect the results. The authors further note that SSRIs have a higher degree of affinity for sigma-1 receptors than do tricyclic ADs, with fluvoxamine having the highest potency. Yet, as we have stated previously, the efficacy of SSRIs and TCAs in humans is very similar, so whether these differences in sigma receptor affinities have any clinical implications is not clear. The authors also note that sigma-1 receptors up-regulate BDNF, the implications of which we have already explored.

With regard to APs, there is a clear relationship between butyrophone structure and affinities for the cloned human sigma-1 receptor, with haloperidol and reduced haloperidol, bromperidol, chlorohaloperidol, and trifluorperidol having high degrees of affinity, as does fluphenazine, but not clozapine. Fluvoxamine had

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approximately the same degree of affinity as did fluphenazine (Lee et al., 2008). However, the authors note that there is a disparity between the ability of these drugs to bind the receptor and their effectiveness as antipsychotics, making it unlikely that the sigma-1 receptor plays a role in the treatment of psychotic symptoms. Given that sigma-1 antagonists diminish the antidepressant effects of sigma-1 agonists, it also is unlikely that the putative antidepressant effects of antipsychotics are mediated by this receptor.

16. Conclusions

Let us assume that additional studies will demonstrate a significant role for APs in the treatment of major depression, and that the number of FDA-approved APs will continue to increase. History suggests that this is inevitable, given the rapid approval of all atypicals for mania. The barrier for approval of a new condition, after all, is flimsy, since the FDA requires only one randomized, controlled trial. We also need to acknowledge that FDA approval for depression will result in a dramatic increase in prescriptions for atypical APs, regardless of their potential for metabolic side-effects.

While one can argue that the most important issue is whether APs are effective in treating depression, the lack of a coherent neurochemical framework for their efficacy is bothersome. Indeed, the precise mechanism underlying the action of many drugs is in doubt, among them ADs, APs, and lithium. Yet, as David Healy pointed out (1977), the search for specificity of disease and treatment is relatively new, and did not make much headway until the advent of bacteriology and the discoveries of Pasteur, Lister, and Robert Koch in the late 19th century. Healy contends that the success of bacteriology led to the 1962 FDA emphasis on randomized, controlled trials, the designation of some drugs as prescription only, and the search for specific drugs aimed at specific diseases.

Yet Healy insisted years ago that this model, while often effective for disorders with demonstrable specific causes, has not worked for psychiatry, with the prime example being the lack of disease specificity with ADs and APs. Given the state of affairs today, with APs being used for schizophrenia, mania, and depression, and numerous off-label conditions (Leslie et al., 2009) including social anxiety (Vaishnavi et al., 2007), and anxiety associated with bipolar disorder (Hirschfeld et al., 2006), his conclusion seems increasingly sound. Were we to examine the foundation for treating mania with the list of modalities mentioned earlier, the problem of non-specificity would loom even larger. At this point, it appears that non-specificity also characterizes the more recent, albeit fascinating work on HDACs and ASICs.

17. What can be done?

Given the market forces and the bond between the drug companies and psychiatry, it seems inevitable that an increasing number of drugs will be approved for an increasing number of conditions, and that polypharmaceutical cocktails will be the norm, despite concerns over the evidence base, drug interactions, side-effects, costs, and a lack of consistency with the goals of biological psychiatry/psychopharmacology. In fairness, whether this development can or should be side-tracked is open to debate.

One could argue, as I mentioned earlier, that if APs and ADs have a variety of non-specific effects that allow them to be efficacious in a variety of disorders which themselves lack specificity, then the goals of the molecular medicine group may not be widely applicable to psychiatry. In that case, one could argue that the efforts of the MMG should be more focused, thus saving valuable time and money. I am not suggesting that the search for genetic factors underlying psychiatric disorders be entirely given up, but I am suggesting that less research money be poured into genetic studies aimed at establishing boundaries between disorders. Indeed, the search for clear lines of demarcation between disorders has paradoxically produced evidence suggesting considerable overlap, especially with regard to major mental illness (Van Snellenberg and de Candia, 2009; Craddock, O'Donovan, Owen, 2009), Holsboer (2008).

Indeed, it seems increasingly obvious that clinicians are actually operating from a dimensional paradigm, and not from the classic paradigm based on specificity of disease or drug. However, should we choose to continue with the specificity paradigm of the past 50 years, the disjunction between those paradigms and our approach to treatment needs to be recognized and investigated. If we are to make progress in clarifying the pathophysiology of psychiatric disorders and the mechanisms by which drugs work, we must have transparency with regard to funding, potential conflicts of interest, do away with publication bias, and insist on unbiased analyses of data. Clinical studies should always include a section on the "why" of the findings, even if speculative. Bench scientists need to be more familiar with current clinical studies, and stop using outmoded clinical research as a basis for drawing conclusions about the relevance of neurochemical processes to drug efficacy. Bench and clinical scientists need to fully address the question of whether the molecular/cellular/anatomical findings, even if interesting and novel, have anything to do with clinical outcome.

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