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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.