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Commentary

Neuropsychopharmacology: Reflections on 40 Volumes

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This issue completes volume 40 of Neuropsychopharmacology (NPP), with the first issue published in December, 1987. This should be distinguished from our 40th anniversary; for the first several years, issues were thin, months were skipped, and multiple volumes were published per year. To commemorate this accomplishment, the editor-in-chief (Dr Carlezon) asked me as in-coming ACNP President to write a brief overview of my views on the developments in our field over this time period, using highly cited articles published in NPP as a guide.

Early on, two articles highlight themes that continue today. One is the development of animal models for psychiatric illnesses. Markou and Koob (1991) developed an animal model of the depression or anhedonia that accompanies cocaine withdrawal, with the drug being self-administered. The use of intracranial-self stimulation (ICSS) thresholds revealed them to be elevated during cocaine withdrawal, with this being interpreted as an 'anhedonic' state due to a desensitization of the reward pathways mediating ICSS reward. The establishment of this model enabled studies to try to understand the neurochemical mechanisms underlying a specific aspect of cocaine withdrawal, with this search continuing to the present.

This article was ahead of its time by focusing on a component of the withdrawal process rather than withdrawal *per se*. Presently, much attention is focused on specific behavioral components of our psychiatric syndromes rather than the complete illness, and this is so both clinically and pre-clinically. This makes sense because our diagnostic schema have no bases in biology and there is considerable symptom overlap among diagnoses, leading to the idea that there is extensive comorbidity in psychiatry- but is that really so? Also, our animal models of psychiatric illnesses, be they developmental, genetic, drug- or environmentally induced, have led to useful insights into neurochemicals, signal transduction pathways and circuits involved in some behaviors, but have not yet led to substantive clinical therapeutic advances. Novel drug targets identified pre-clinically have in general not panned out in the clinical arena. Some of this, though, may be because our clinical trial methodology has not followed in concert with pre-clinical advances such that most efficacy studies still lump together what are heterogeneous groups of patients. One might say how can we subdivide in the absence of biomarkers, which do not exist? But one might also ask how can we hope to find a biomarker among a group of patients that might have 3, 7, or 10 different pathologies, all leading to the same behavioral output. Talk about the chicken and the egg!

Another theme that continues into the present is the time-dependent, downstream consequences of acute actions of some type of psychotherapeutic drugs that correlate better with optimal clinical improvement. Chaput *et al* (1991) reported that various types of antidepressant treatments (ECS, imipramine, paroxetine), when given for 14–21 days, increased serotonergic transmission by different mechanisms, all of which involved changes in serotonergic receptor sensitivity. Papers such as this led to clinical trials of 5-HT_{1A} receptor antagonists to try to enhance the effectiveness of SSRIs. Unfortunately, that strategy has not proven useful, possibly because the drug most widely studied, pindolol, may not block 5-HT_{1A} receptors effectively at the doses employed. This so-called 'target engagement' issue is now a key facet of clinical studies. Even if the target is engaged, though, clinical trial methodology may hamper our ability to detect early improvement, if it occurs; efficacy studies are now almost exclusively done using out-patients and oftentimes the first time the patient is assessed after treatment starts is at least one week. Onset of action studies require different methodology from standard efficacy studies. Of course, in this arena ketamine has been fortuitous. Academic clinical research studies showed it to have rapid efficacy in treatment-resistant depression; further, its initial mechanisms of action are distinct from those of traditional antidepressants. One hopes that it may be a key to unlocking the mysteries of early clinical improvement.

In the mid-1990s, there was great interest in the development of 'atypical' antipsychotic drugs following earlier studies demonstrating efficacy of clozapine in treatment-resistant schizophrenic patients. A highly cited paper by Beasley *et al* (1996) was a 6 week clinical trial of the efficacy of olanzapine in schizophrenic patients, with the comparators being both placebo and haloperidol. This multi-center trial, which continues to be *de rigueur* for clinical trials, compared the effects of various doses of olanzapine. The two higher doses of olanzapine as well as haloperidol were

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superior to placebo in reducing symptomatology. As expected, there were less extrapyramidal side effects with olanzapine than with haloperidol. A limitation of trials such as these is their relatively short duration. No mention is made in the paper of olanzapine-induced metabolic adverse effects such as obesity or type II diabetes which are now recognized as a later-developing serious problem with several of these drugs. These types of trials remain the mainstay of studies attempting to show efficacy (and adverse effects) of newly developed psychotherapeutic agents. Only more recently, as mentioned, are trials being developed to evaluate efficacy for certain dimensions or domains of psychiatric syndromes. Of course, pharmaceutical companies have to answer to regulatory agencies with respect to approval of their drugs. What use is there in carrying out expensive clinical trials if the data obtained will not be considered as part of the approval process? Better drug development will depend not only on cooperation between various types of research scientists but also the education and cooperation of regulatory agencies. And the ACNP can and should play an important role here.

Cognitive processes as related to psychiatric illnesses have long been the purview of psychiatry, e.g., Freud and dreams. The seminal work of Beck and associates in the 1970s on cognitive therapy provided a great impetus to the study of cognition. And this led to much basic research separating cognition into various components. In 1999, Rogers *et al* (1999) published a highly cited study about decision-making cognitive processes in chronic amphetamine or opiate abusers. Whereas the amphetamine abusers made sub-optimal choices and deliberated longer to make their choices than healthy volunteers, the opiate abusers only differed in the time it took them to make their choices. Such changes were similar to those found in this study in patients with damage to the orbitofrontal PFC but not other regions in the PFC. Further, healthy subjects given a low tryptophan drink, which may have led to reductions in brain serotonin, had qualitatively similar deficits in decision making as those of the amphetamine abusers. This study, then, identified both a brain area and a neurotransmitter that may be involved in a specific cognitive process in humans, with such themes continuing today. Indeed, among the hottest areas in neuroscience and in psychiatry presently is the study of cognition from many vantage points.

Investigations of the possible involvement of immune system dysfunction in the pathogenesis of depression began in the 1980s and despite or perhaps because of considerable conflicting results this area remains very topical. One interesting aspect of such studies was the observation that patients given immunotherapy with interferon-α (IFN-α) can develop neuropsychiatric symptoms, particularly ones associated with depression. In a seminal study from the Miller lab (Capuron *et al*, 2002), IFN-α treatment in patients with malignant melanoma produced symptoms such as depressed mood, anxiety, and cognitive dysfunction later in treatment. Concomitant treatment with paroxetine was found to reduce the expression of such symptoms. This report not surprisingly led to attempts at replication. Again not surprisingly, although not all confirmed the utility of using an SSRI, several did and this practice is now used to mitigate these debilitating symptoms. It is a nice example of a research finding leading to an innovative clinical intervention.

After deep brain stimulation was shown to be effective for movement disorders, particularly those associated with Parkinson's disease in the 1990s, this approach began to be evaluated for psychiatric illnesses. Following a study for DBS in depression first published elsewhere in 2005, two highly cited papers appeared in NPP. One studied its effect in 10 patients with treatment-resistant OCD (Greenberg *et al*, 2006) and the other in three patients with treatment-resistant depression (TRD) (Schlaepfer *et al*, 2008). In the open study with the OCD patients, stimulation of the ventral capsule/ventral striatum resulted in a significant reduction in the severity of symptoms and global functioning and this occurred in eight of the patients followed for at least three years. For those patients with TRD, stimulation of the nucleus accumbens resulted in a rapid decrease in depressive symptoms. Although the number of patients studied in each trial was quite small, these were promising results, especially in these very treatment refractory patients. Overall, the results of DBS for OCD seem quite promising with various brain regions targeted, all of which are part of the orbitofrontal-striatal-thalamo-cortical (CSTC) circuit. Importantly, efficacy has been reported in multiple double-blind controlled studies. DBS for TRD has also targeted various brain regions. There have been less controlled trials in depression than in OCD and the results of those lend less enthusiasm for its results in depression. Nevertheless, it is clear that some patients with TRD respond very beneficially to DBS. Unfortunately at present, we do not yet have the means to distinguish those who will from those who will not, as is so for psychotherapeutic drugs as well. Clearly, much more research is needed in this area as resistance to treatment for patients with psychiatric illnesses remains a very serious problem. The use of various stimulation modalities has become a very active area of investigation with great promise for certain patients.

The demonstration of neurogenesis in the adult brain in the mid 1990's led to much research examining its importance in both the development of psychiatric diseases and the mechanism of action of psychotherapeutic drugs. Malberg and Duman (2003) reported, in agreement with earlier results, that exposure to stress produced both a depression-like behavioral deficit and a decrease in cell proliferation in the hippocampus. Importantly they also showed that repeated treatment with fluoxetine attenuated both the stress-induced behavioral deficit and reversed the decrease in cell proliferation. This type of study, and even earlier ones, were important in rethinking the mechanism of action of many psychotherapeutic actions from an emphasis on acute synaptic events to the production of somewhat delayed but more sustained morphological changes triggered by their acute actions. However, the rapidity of the antidepressant efficacy of ketamine does bring into question the necessity of enhanced neurogenesis for antidepressant efficacy.

Somewhat noteworthy has been the absence of highly cited publications in NPP of key genetic findings with respect to the illnesses themselves or to their treatment with drugs. It would be remiss not to mention the importance that such results have had on our field, e.g., functional genetic variants that predict emotionality and cognitive function, others that

predict risk of addictions and still others for treatment response (personalized medicine). Many believe that genetics will provide key answers to some of the most important questions remaining in psychiatric research. Hopefully, in the future investigators in these areas will publish some of their key results here in NPP.

These and many other articles show that NPP has fulfilled the high hopes that the ACNP had when founding it, namely that it would publish some of the key research findings in our field. Further, its emphasis should be on both preclinical and clinical research as the integration of such types of studies has long been the cornerstone of the ACNP. Indeed, one could claim that the ACNP was 'translational' before the term was coined. A pessimist might say that in spite of this great research, we still do not have a firm understanding of the pathogenesis of psychiatric disorders nor, from the perspective of efficacy, are our treatments superior to those we had in the late 1980s. But trying to relate the initial cellular effects of a drug to behavioral benefit in heterogeneous patient groups is a very difficult task. Let's not forget that at the basic science level, it takes years to figure out the intermediate processes involved when an endogenous ligand activates a receptor and its ultimate cellular effect. And then, just when we think we have it figured out, additional layers of complexity for the effects of drugs become evident such as agonist-directed trafficking or the fact that cell phenotype is not a constant.

By contrast, an optimist, such as I, might say, 'give me a break!' We are trying to understand the brain, the most complex organ in the body and the one that gives us our individuality. It has about 85–100 billion neurons (and more neuroglia), which is about 25–100% of the stars in the Milky Way! So we are truly reaching for the stars when we attempt to understand both normal and abnormal brain function! We are still developing the tools to understand its normal function, particularly on the very, very short time-scale by which neurons transmit information. In spite of such difficulties, the effectiveness of our drugs, although moderate, are comparable to those in other fields of medicine in spite of our being a 'younger' science (Leucht *et al*, 2012). Exciting new techniques and approaches are facilitating greatly our ability to understand the functioning of circuits in the brain and even that of individual cells. Although change has been slow in coming, it is coming both with respect to diagnoses and the design of clinical trials. There is no doubt that NPP will be at the forefront of publishing these exciting new results which will eventually have a substantial positive impact on the lives of our patients.

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