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Pro-convulsant effects: A neglected dimension of psychotropic activity

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Introduction

When the modern psychopharmacological era began in 1954, there were broadly speaking two therapeutic principles – stimulants and sedatives. Stimulants in general had formerly been known as tonics. It was only with the arrival of the amphetamines that the word stimulant came into use. This group encompassed tonics, psychic energizers and stimulants. The sedatives included sedatives, major and minor tranquillizers, hypnotics and later anxiolytics and others.

There were vigorous efforts to fit the new drugs – which seemed to have greater specificity than the older drugs had – into this binary classification. Terms like neuroleptics, psychoanaleptics, psychodysleptics, thymoleptics and others proliferated (Healy, 2002).

The efforts to classify the new agents were married to new fields of basic research which looked at the effects of these drugs on systems such as the reticular activating system (RAS). It became clear that the same outcome could in some cases be produced by stimulating or sedating the RAS. Anaesthesia, for instance, is classically induced by sedatives but it can also be induced by disinhibiting or stimulating agents such as ketamine or phencyclidine.

This neurobiological research converged on a strand of psychobiology that in the early 1950s found its fullest expression in Eysenck's psychology of individual differences. The impetus for this research came from Pavlov who, faced with dogs with what he termed traumatic neuroses following a flooding in his laboratory in St Petersburg, found that some responded to stimulants while others, with what superficially appeared to be the same condition, responded to sedatives (Healy, 2002).

Stemming from this, Eysenck and others proposed that successive layers of inhibitory reflexes produce the personality dimensions of extraversion and introversion. The Eysenck Personality Questionnaire, Cloninger Tridimensional Personality Questionnaire and most other personality questionnaires we have today map these dimensions and all claim a biological validity (Eysenck, 1963).

Early findings from Eysenck's laboratory showed that introverts and extraverts could be distinguished on the basis of their response to sedatives. Degrees of introversion and extraversion, for instance, can predict the dose of anaesthetic agent needed to induce sleep for surgery. Introverts and extraverts show differences on a large raft of neuropsychological tests (Claridge, 1972, 1996).

This line of thinking was eclipsed for four reasons. First the new antidepressants and antipsychotics appeared to be more categorical than dimensional in their effects. Second, with hypotheses like the catecholamine hypothesis of depression and dopamine hypothesis of schizophrenia, these drugs were recast as magic bullets rather than therapeutic principles. Third, the new drugs that acted on multiple brain systems embodied more than one therapeutic principle, making them unsuitable to fit into a dimensional classification system.

Finally, convulsions were a notable hazard of the tonic group of drugs. Tonics like strychnine were outright convulsive agents, others like camphor were pro-convulsant, where the later stimulants such as amphetamine were not.

The anticonvulsant effect

The new drugs brought an increasing drive to specificity in psychiatry so that even the stimulants were captured and transformed into a specific treatment for attention deficit hyperactivity disorder (ADHD).

The work of Ballenger and Post and others around 1980 marked a further defining moment in the move from therapeutic principles to magic bullets (Ballenger and Post, 1980; Post, 2000). Before that anticonvulsants such as carbamazepine and sodium valproate were known to have beneficial effects in mental states but these were largely attributed to anti-impulsive or other functional effects (Harris et al., 2003). They were viewed as offering some ill-defined therapeutic principle.

In the early 1980s Post and colleagues proposed that mood disorders might resemble epileptic disorders such that one episode might kindle further episodes. If so a goal of

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treatment was to suppress kindling. The beneficial effects of carbamazepine and sodium valproate were reinterpreted in these terms and laid the basis for the concept of mood stabilization (Silberman et al., 1985; Post et al., 1986).

This proposal supported the introduction of a range of anticonvulsants to the market as 'mood stabilizers', a concept that had not existed before that. It also created the concept of a mood stabilizer that is a magic bullet rather than therapeutic principle concept.

Magic bullets or therapeutic principles?

The domination of specificity in recent years means that drugs are seen as magic bullets remedying a pathophysiological process, without any intervening benefits, when in fact antipsychotics were once called major tranquillizers and SSRIs exert a generic anxiolytic effect. These latter effects may well be the primary effects that either are or are not therapeutic in individual cases. Such an effect can be termed a therapeutic principle. Some treatments such as tricyclic antidepressants may embody more than one therapeutic principle, namely a vigilance-enhancing effect on the norepinephrine system and an anxiolytic effect on the serotonin system.

In the case of dopamine receptor antagonists, actions on different parts of the dopamine system may lay the basis for antitussive, antipruritic, antiemetic and tranquillizing therapeutic principles and it can be possible to optimize for one or other of these principles but rarely for more than two in the same molecule.

Concealment by RCT?

The randomized clinical trial (RCT) process through which new agents now enter clinical use tends to conceal differences between treatments. As a result, a wide variety of agents with quite diverse effects, such as antipsychotics and differing anticonvulsants, are all classed as mood stabilizers even though these drugs have very different functional effects – they embody very different therapeutic principles. In the same way trials for antidepressants conceal rather than reveal the differences between agents selective to the norepinephrine or the serotonin system.

Even though anticonvulsants are primarily sedative agents, their use now is disease specific rather than temperament based. In the case of patients with a bipolar disorder that seems unresponsive to one anticonvulsant, the general approach has been to add further mood stabilizers to the mix on the basis that these are all specific to the illness. However, this in principle is like Pavlov giving all his dogs sedatives and adding further sedatives if they failed to respond to the first, rather than stopping the sedative principle and giving a stimulant instead.

Where once we recognized that treatments might work on constitutions rather than illness processes or might work on both, over the past 30 years there has been an increasing emphasis on illness processes and, with the exception of stimulants for ADHD, an emphasis on sedative agents.

This has meant in practice a gravitation toward sedatives, where once the premium in mental health was on tonics. Recent antipsychotics have been more sedative than many of the first generation of antipsychotics. The antidepressants once comprised a mixture of stimulant MAOIs and sedative tricyclics. The SSRIs are more broadly serenic or anxiolytic agents.

In the case of childhood disorders, the move to treating ADHD with stimulants has brought in its wake claims that bipolar disorder comes in juvenile forms and these are best treated with sedatives. The sequence often appears to be that the child is first treated with stimulants and if they fail to respond they are re-diagnosed with bipolar disorder and given a more sedative agent. One parsimonious way to account for this is that, rather than entities such as ADHD or bipolar disorder, which may also exist, in many cases we are seeing children with very similar clinical presentations but different constitutional types of whom some respond to one therapeutic principle, a stimulant, and others to another, a sedative (Healy, 2008).

A pro-convulsant therapeutic principle

Among the antipsychotics, one treatment stands out – clozapine. This is generally held to have unique benefits. There have been significant efforts to replicate its benefits without its headline risk of agranulocytosis. One approach has been to produce molecules almost identical in structure to clozapine (quetiapine, olanzapine). Another has been to reproduce clozapine's receptor profile (risperidone, ziprazidone, sertindole). The consensus is that, while many of these medications have benefits, none reproduce clozapine's unique benefits (Healy, 2002).

Clozapine comes with other risks besides agranulocytosis, in particular a risk of convulsions. No-one has attempted to optimize for its pro-convulsant properties. This is regarded as a side effect to be eliminated. Quetiapine, for instance, is anticonvulsant and interferes with ECT where clozapine enhances ECT (Braga and Petrides, 2005).

Within the mood-stabilizer domain, the standout clozapine-like drug is lithium. There is a consensus that while many anticonvulsants can be beneficial in bipolar disorder, none produce the quality of responses seen in many patients with lithium. Lithium, like clozapine, is pro-convulsant.

Finally, ECT is unique across psychiatry in producing benefits in patients who respond to no other conventional agents.

Ketamine: a convulsant?

There is at present interest in the possible antidepressant effects of ketamine, a glutamate *N*-methyl-d-aspartate (NMDA) receptor antagonist. Berman

et al. (2000) reported an antidepressant effect of ketamine in a randomized placebo-controlled trial. Since then nine other studies, mainly of treatment-resistant depression with small sample sizes, have yielded similar findings (Murrough, 2012).

These trials, however, give no idea what kind of patient might respond to ketamine-like drugs. Based on the precedent of the SSRIs, companies are likely to seek the broadest possible market and try any new compounds in a mixture of depressive states rather than depressive psychoses and related states. This will likely lead to evidence of benefit but will also leave clinicians in the dark as to what kind of patient might benefit most from the treatment.

The mechanism underlying ketamine's putative antidepressant effect is unclear. Antagonism of the NMDA receptors has resulted in 'antidepressant' effects in preclinical studies (Murrough, 2012), but preclinical studies reveal little. Trials of an NMDA receptor partial agonist GLYX-13 have led to claims that it produces antidepressant effects without the dissociative or psychotomimetic effects accompanying ketamine (Burgdorf et al., 2013). Similar claims have been made for ADZ6765 (Zarate, 2012). While the focus is on the NMDA receptor, it should be noted that ketamine has effects on other systems, and these effects might produce some clinical benefits without a distinctive NMDA receptor effect.

What do these findings mean? While it is useful to exclude dissociative or hallucinatory effects, if possible, the key question is what property should developers attempt to optimize in order to produce a benefit in some mood disorder?

Ketamine has two effects of note. It is a stimulant-tonic. The basis for calling it a stimulant lies its effects on the RAS. It also shares a pro-convulsant property with clozapine, lithium and ECT, although it is not clear all four agents act through any common ionic channel to produce their effects.

While the focus of antipsychotic and mood-stabilizer development has been on structures and receptors it has not been possible to optimize for an action on ionic channels that would make a drug more or less convulsant. This is a neglected channel of drug development.

The treatment-resistant cases currently going through depression trials with ketamine or its analogues are likely to be a mixture of clinical pictures from psychotic depression to neurotic states. If ketamine's pro-convulsant properties are important, one might expect melancholic patients to respond to it but not more neurotic cases. If analogues that are developed lack a pro-convulsant effect in contrast, one might predict they will be less likely to show effects in melancholic states.

In the case of drug development to date, there has been no effort to optimize for pro-convulsive effects. There are a number of candidate molecules to work from including ketamine, clozapine, lithium, camphor, pentylenetetrazol, picrotoxin, bemegride, buproprion and fluoroethyl.

Many of these drugs can have effects in addition to being pro-convulsant. Thus lithium seems to have an anti-impulsive effect in addition to being pro-convulsant. Clozapine has a number of psychotropic effects in addition to being pro-convulsant and ketamine may be an abreactive agent in addition to being pro-convulsant. Buproprion also works on catecholamine systems.

These different effects in the one molecule may support beneficial effects in quite disparate conditions but if the practice of therapeutics is to be rational, doctors need to know what they are doing rather than simply prescribing something because it has been shown to be 'antidepressant'.

A hypothesis and tests

The distinction between dimensions and categories in psychiatry is as fundamental as that between waves and particles in physics and probably as irresolvable. This is compounded in this case by the fact that drugs like ketamine may do more than one thing, one of which might be categorical or specific and the other dimensional and non-specific.

Our hypothesis, based on clinical experience treating severely depressed patients with ketamine, is that ketamine will have benefits in melancholic depression stemming from its pro-convulsant effects. This hypothesis originated from a successful use of ketamine in two patients with severe bipolar depression with a history of responsiveness to ECT and lithium, but a poor or no response to an extensive range of other agents. Both patients responded after a single infusion of ketamine100 mg, and their recovery has been maintained. In contrast severely depressed patients with a history of non-response to ECT in our clinic have not responded to ketamine.

If this hypothesis holds true the development of compounds that will truly mimic the effects of ketamine will only be successful if these compounds are pro-convulsant. We predict that depressive psychoses will not respond to ketamine-like NMDA receptor antagonists that are not pro-convulsant.

Ketamine-like agents that are not pro-convulsant may well have beneficial effects in other depressive disorders. If so this will stem from a different therapeutic principle and it will be important to establish just what such agents may be doing in other types of depression.

If correct, this hypothesis also calls for tests of ketamine and for ketamine-related compounds in benzodiazepine-resistant catatonia and neuroleptic malignant syndrome (NMS) where ECT might ordinarily be used. We would predict that pro-convulsant compounds would be helpful while compounds that are not pro-convulsant will not be in these other conditions also.

More generally the hypothesis calls for efforts to develop compounds with pro-convulsant effects and an

attempt to establish what effects such a therapeutic principle has and who benefits.

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