EDITORIAL

Rhyme or reason in therapeutics

John Cookson & Jonathan Pimm

John Cookson is a consultant in general adult psychiatry at the Royal London Hospital and at Tower Hamlets Centre for Mental Health, Mile End Hospital, East London NHS Foundation Trust, London, UK. He trained in physiology and pharmacology at the University of Oxford and he has a career-long interest in psychopharmacology. **Jonathan Pimm** is a consultant in general adult psychiatry employed by the East London NHS Foundation Trust, London, UK. He completed an MD under the supervision of Professor Hugh Gurling looking at transport mechanisms at the synapse. **Correspondence** John Cookson. Email: john.cookson1@nhs.net

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SUMMARY

This editorial introduces the *BJPsych Advances* special issue on biological psychiatry.

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As the bewildered slave Dromio complains in one of Shakespeare's earliest plays, our actions need 'rhyme or reason' or we are lost in a 'comedy of errors'. In his case the error arose because two people who appeared identical were different.

Many treatments in psychiatry have proven efficacy. However, clear, understandable and scientific explanations of how they work are thin on the ground. In short, we have much rhyme but little reason. Several of the articles published in this special biological psychiatry issue of *BJPsych Advances* attempt to redress this.

Specifically, in the quest for reason, identification of drugs' molecular targets has been crucial; so too the concept of receptors for neurotransmitters. The articles we have chosen cover a smorgasbord of important topics, including drug–receptor interactions in depressive illness and the expert use and side-effects of antipsychotics, lithium and ECT.

Lithium and clozapine

Lithium has numerous molecular targets but potentially its most devastating effect is on cerebellar granule neurons during episodes of toxicity. Murphy et al (2023) review the management of lithium toxicity. All doctors should be aware of the signs of toxicity that require immediate cessation of lithium (vomiting, cerebellar signs or impaired consciousness) and the situations that may lead to it.

Clozapine can be difficult to manage, and therapeutic drug monitoring (TDM) can be helpful. Many factors influence blood levels. Flanagan et al (2023) highlight the profound effects that smoking cigarettes can have. Just seven cigarettes a day can induce enzymes that will metabolise clozapine, necessitating a doubling of dose. Conversely, admission to a smoke-free unit and then commencement of leave, when the patient may have the opportunity to take up the habit again, will play havoc with clozapine levels. Much can be learned from the ratio of clozapine to its active metabolite norclozapine. Drug interactions and the effects of inflammation from infection are also important. Discerning patients' ability to metabolise a drug may assist prescribing: genetic testing to identify fast clozapine metabolisers should be considered.

Genetics and psychiatry

The potential benefits of pharmacogenetic testing in psychiatry are touched on in Lindsay Mizen's scholarly review (Mizen 2023). Specifically, to explore patients' likelihood of responding favourably to various medications and to predict the possibility of experiencing side-effects, an in-depth knowledge of genetics will become increasingly important. Mizen clears a way to understanding the benefits and risks of testing patients' genomes and provides an insight into how geneticists decide whether DNA variants are pathogenic.

Magnetic seizure therapy does, at cursory glance, appear to be a potential alternative to ECT for treatment-resistant depression. However, on closer inspection there have been no comparisons with sham therapy and its efficacy is therefore questionable, as our look at a Cochrane Review on the intervention concludes (Glatzel 2023).

Depression

Alexander & Young (2023) review new pharmacological treatments for depression. In explaining their mechanisms of action they focus on subtypes of serotonin receptors and locate these in particular pathways in relation to vortioxetine and psilocybin. They also consider the role of glutamate, opioids and γ-aminobutyric acid (GABA) and to a lesser extent catecholamines, particularly noradrenaline, in antidepressant effects. With much hype surrounding the use and monetisation of psilocybin and ketamine the review is apt. They conclude that the potential benefit of psilocybin is 'still, effectively, hypothetical and the hypothesis should be tested using phase III RCTs'. (A study by Goodwin et al (2022) published after Alexander & Young had written their article has contributed to this.) They touch on inflammation as a novel target in treating depression. Their tempered conclusion is that the 'landscape of novel pharmacological agents for the treatment of depression is vast and varied' and is essentially a work in progress. Ways to manage the adverse effects of these repurposed psychotomimetic drugs need also to be addressed.

Autism spectrum disorders

The increasing number of in-patients having 'autism spectrum disorder' as part of their diagnosis makes the review of treatment by Carthy et al (2023) very timely. Written from the perspective of a high-security hospital, it discusses current classifications and highlights the wider range of indications for risperidone and aripiprazole by the US Food and Drug Administration (FDA) under the label of pervasive developmental disorders. Within the treatment of comorbid psychiatric disorders in people with autistic features, it explains that so-called pseudo-hallucinations can be responsive to antipsychotics.

Finally, to add further reason to the rhyme of prescribing antipsychotics, a series of papers address the use of partial agonists at dopamine receptors and alone or in combination with other antipsychotics (Cookson 2023a, 2023b, 2023c, 2023d).

Partial agonism of dopamine receptors

The concept of agonistic and antagonistic drug–receptor interactions has proved amenable to mathematical analysis, by applying the principles of physical chemistry (the law of mass action) to interactions of drugs with theoretical 'receptors' (see Rang 2006). However, partial agonism is more complicated.

Psychiatrists have become familiar with the antecedents of relapse of psychosis: the discontinuation or reduction of antipsychotic medication, the escalating misuse of cannabis or cocaine. However, recent years have seen different patterns of precedents to relapses and admissions: people with side-effects such as weight gain, drowsiness or sexual impotence who have been prescribed the partial agonist aripiprazole either as an adjunct or a replacement for the previous antipsychotic and who have subsequently relapsed. Furthermore, other patients had done well on aripiprazole either as monotherapy or in combination. An explanation, beyond simply describing aripiprazole as being 'only' a partial agonist, was needed.

In this issue, the explanation is given in four parts. The first sets out the basic principles of drug–receptor interaction at a molecular level in the context of the dopamine hypothesis and the treatment of schizophrenia, including the phenomenon of partial agonism (Cookson 2023a). The second summarises the pharmacological properties, clinical uses and side-effects of the three main partial agonists of dopamine receptors – aripiprazole, brexpiprazole and cariprazine (Cookson 2023b). The third discusses the use of a combination of two antipsychotics in the treatment of schizophrenia, using a formula and applying data from positron emission tomography (PET) scans showing occupancy by various antipsychotics (Cookson 2023c). And finally, the fourth culminates in the application of the same formula to the combination of a full antagonist with a partial agonist (Cookson 2023d).

We accept that this approach has many limitations. Our aim was simply to provide theoretical underpinnings that might assist clinicians in making decisions about doses of antipsychotics – including partial agonists – either alone or in combinations.

We hope that overall this issue adds to the reasoned basis for prescribing.

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