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Book review

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Next Generation Antidepressants. Moving Beyond Monoamines to Discover Novel Treatment Strategies for Mood Disorders. Edited by C. E. Beyer and S. M. Stahl. (Pp. 150; £50.00; ISBN 9780521760584 hb.) Cambridge University Press: Cambridge. 2010.

Next Generation Antidepressants is an edited volume with individual chapters written by scientists working in the field of drug development, as well as basic researchers seeking to understand the aetiology of affective illness. The book comprises eight chapters and is aimed at an audience of mental health clinicians, prescribers and researchers and in particular psychopharmacologists seeking to learn contemporary trends and issues regarding antidepressant treatments. The basic rationale for the book goes as follows: depressive disorders are a major public health problem; current antidepressant drugs are effective only in a limited number of patients; they are limited by a delayed onset of efficacy, treatment resistance and deleterious side-effects. Thus it is argued there is an urgent need to develop novel effective pharmaceutical therapies. Throughout this book, these arguments are repeated often. It is optimistically implied that this field is at a tipping point, and the next ten years will see great changes in the efficacy of available antidepressants. I will give a brief synopsis of each chapter, later followed by a critical discussion of the book as a whole.

The opening chapter by Mignon and Stahl provides a concise overview of the current landscape that is also discussed in greater depth in later chapters. To paraphrase here, historically there has been a reliance on monaminergic treatments to essentially increase the levels and synaptic effects of serotonin, dopamine and noradrenaline. Recent large-scale studies such as STAR*D have demonstrated that these current treatment options are ineffective for the majority of patients. Ways to improve treatments as briefly touched on in this chapter include investigating new formulations of old drugs, more selective compounds and the use of new drugs such as triple reuptake monamine inhibitors. A final point raised in this chapter is that a potential reason for the lack of treatment response in patients with unipolar depression has been as a result of the misdiagnosis of other disorders, e.g. bipolar II disorder. In fact the conceptually 'messy' question as to what a depressive disorder actually is draws a long shadow over the book as a whole, and I return to this later in the review.

Chapter 2 by Dremencov and Cremers goes further into novel therapeutic targets for treating affective disorders. One of the problems of an edited volume by different authors such as this is the repetition of material. Many of the key justifications for new antidepressants are again repeated in this chapter but discussed further, i.e. the benefits of selective serotonin reuptake inhibitors (SSRIs) over tricyclic antidepressants. Again new strategies for improvement of antidepressants treatments are further presented, as examples: ultraselective SSRIs, selective norepinephrine (NE), dual- and triple-reuptake inhibitors; and treatments that work through other neurotransmitter/hormone systems or through altering hypothalamic-pituitary-adrenal (HPA) axis function. Such treatments currently under clinical development are tabulated and usefully summarized in this chapter.

Chapter 3 by de Groote *et al*. describe the development of novel animal models of depression. They depict a clear problem in that when many drugs that have demonstrated efficacy in animal models reach 'patients', they fail in initial trials and therefore do not make it into the real world. de Groot *et al*. suggest the investment and adoption of novel technologies such as scanning and *in-vivo* monitoring, amongst others, are critical to the translation of animal models for clinical use.

Relatedly, translational research based on imaging technologies is the focus of chapter 4 by Shamy *et al*. This chapter argues for the use of biomarkers, revealed through fMRI (functional magnetic resonance imaging) and PET (positron emission tomography) imaging to more reliably predict drug effects and treatment outcome in patients. The authors of this chapter focus on disease biomarkers relevant to investigating depressive disorders: negative bias and cognitive deficits, and their respective neural substrates. The authors argue that neuroimaging can be used to distinguish between patients with either cognitive or affective biases within a clinical trial. I think such aims are wishful thinking, simply as mood disorders cannot be dissected in this way.

However, I do believe that the actual translation between mental and neural phenomena in this chapter is a critical and much needed development in the field. Although neuroimaging is a hugely expensive technique, it has revolutionised psychiatry with the ability to visualise the neurophysiological basis of the symptoms of extreme emotional distress. As a tool to

understanding the mechanisms underlying mood disorders in order to generate a complete theory of their aetiology, neuroimaging techniques will prove invaluable. As to whether they can be used to enhance patient selection for clinical trials, as proposed in this chapter is very much a tentative proposal at present.

As mentioned previously, one problem for current researchers in the field of mood disorders is what actually constitutes 'major depressive disorder'. There is a case that it has become separated from any tractable basis in psychology or cognitive/affective neuroscience. Such fuzzy nosology has led to great interest in identifying depressive 'endophenotypes' – intermediate phenotypes hypothesized to lie within the aetiological link between genes and clinical disease. In chapter 5, Berghorst and Pizzagalli evaluate the use of the endophenotype concept, as applied to anhedonia, one putative potential endophenotype. The authors conclude from their review that there is limited support at present for anhedonia as a depressive endophenotype based on the criteria of clinical and biological plausibility, specificity, state-independence, heritability, familial association and co-segregation. The authors further conclude that utilizing such an endophenotypic approach would ultimately enhance our ability to design more effective treatment and prevention strategies, although it is premature to conclude too much from the mixed evidence in the literature. Not everyone in the field (e.g. Flint & Munafo, 2007), as acknowledged in this chapter, agree with the benefits of this approach over standard clinical classifications, particular with state/trait and developmental aetiological aspects of depressive disorders but at least they are tractable aspects of the disorder that can be objectively studied.

While psychiatry professionals and researchers believe that depressive disorders run in families, the specific genetic and environmental contributions for this are hotly debated and a focus of much current work. Chapter 6 by Perlis succinctly summarizes the twin, adoption and genetic studies that may illuminate why depressive disorders run in families. Recent genetic literature covering association (candidate and genome-wide), and epigenetic studies is the main focus of this chapter. Again, despite being such a fertile and rapidly developing area of research, the take home message from this chapter is that it is still early days and no specific genetic loci for depressive disorders have been convincingly demonstrated.

The focus of chapter 7 by Rotella is related to chapter 2 in specifying advances and challenges in the understanding of the medicinal chemistry underlying antidepressants. Much of the material in this chapter mirrors that covered in chapter 2, with the addition of diagrams demonstrating the chemical structure of novel potential antidepressants.

The final chapter describes the application of pharmacogenomics and personalized medicine for the care of depression. The much needed integration of personalized medicine into psychiatry has not yet taken place and raises a great number of practical, ethical and financial questions. As stated in the book's premise, current antidepressant drugs are effective only in a limited number of patients. There are a number of reasons for this, but the end result in treating a patient is often a 'trial and error' approach to the selection of drug and dose. I very much enjoyed this chapter as it provided a sobering perspective on the issues and challenges pertaining to the adoption of personalized medicine in healthcare.

I should probably declare at this point, that as a research psychologist conducting neuroimaging research in the affective disorders, I may not be representative of the readership at which this book is primarily aimed. After reading this book, I had a number of thoughts. One thought was ultimately, what do we want our antidepressants to do? The old view, that mood = chemistry, and low mood is caused by a chemical imbalance of serotonin and other monoamines is hopefully left behind. Is it theoretically possible to have a silver bullet or panacea for a major depressive episode? Do we want our novel antidepressant medications to treat different symptoms of the illness, e.g. increasing dopamine for reward, noradrenaline for altering arousal levels and serotonin for reducing anxiety? Obviously believing this implies there is agreement that these neurotransmitters simplistically correspond to such functions (with which I must declare that I do not agree). However, this end point is not clearly articulated in this volume. Do we want to treat the causes of extreme emotional distress or only the symptoms? Is it possible to do something more with a drug, or is this coming into the realms of a 'Brave New World' style soma? Do we want to bring people up to 'normality' with medications or do we want to do something more and provide cognitive and affective enhancement.

An alternative view, to the chemical imbalance explanations that is briefly touched upon in chapter 4 (p. 58), is that we need to ultimately increase cellular resilience and integrity, that at the psychological level, that facilitates learning and consequently an increased ability to adapt to the environment. This view has been argued by psychologists and neuroscientists, e.g. LeDoux (2002). It may be that the current or any generation of antidepressants increase cellular plasticity that allows at the psychological level the ability to un/re-learn negative affective associations with environmental stimuli. Therefore I think this book is

missing a chapter on the neuropsychological aspects of antidepressant drugs. Although neuropsychological aspects are touched on in chapter 5 on translational research in mood disorders, much more detail about this is needed and I think would be very informative to readers.

Another assumption in the book is that such current treatments are limited by a delayed onset of efficacy. However, there is a growing body of evidence that this is simply not the case, as although it may take 4–6 weeks for the remission of depressive episode, changes in mood can be detected more quickly with experimental tests (Taylor *et al*. 2006; Pringle *et al*. 2010). I find it surprising that such evidence is not covered in this book as it has pretty big implications for the book's rationale. These studies suggest that novel antidepressants may not differ from the current generation in speed of effective treatment; it may be that current antidepressants are good enough at reducing 'emotional distress' and then other adaptive psychological mechanisms take place to increase positive affect. Thus it is an open question whether current generation medications are good enough when combined with other forms of therapy. Therefore, instead of health providers purchasing newly licensed drugs they could invest in better research into combinations of old drugs and therapy, as well as research into mood-disorder onset and relapse prevention.

Extending this idea – I would also like to see the financial arguments/health economics that next-generation antidepressants would be more cost-effective than current antidepressants. If this cannot be demonstrated, then health professions would be encouraged to put their funds to better evidence-based use. The current trend is for pharmaceutical companies to withdraw from antidepressant drug development (Miller, 2010); GSK Chief Executive Andrew Witty was quoted as saying that pain, depression, and anxiety were areas where 'we believe the probability of success is relatively low, [and] we think the cost of attaining success is disproportionately high'. Therefore, the book's editors may be more optimistic than the CEOs of drug companies with regard to the development of new central nervous system drugs.

The last argument justifying the need for novel antidepressants concerns the deleterious side-effects of current antidepressants. This is a valid concern but it may be a fact of life that any medication will bring about a range of side-effects, simply because the neurotransmitter systems that they seek to augment have such a wide range of homeostatic functions. It remains to be seen how many of the medications currently under clinical development will actually make it to market due to an improved side-effect profile.

Other minor problems with the book include annoying differences in reference styles across chapters, and chapter 4 references appearing to be out of synchronization with the main text. It is my view that such errors should have been corrected during proof reading.

If I were to be asked whether we are on a tipping point to understanding the aetiology of depressive disorders, the answer would have to be a resounding 'yes', but this would be based on advances in knowledge of genetic and environmental risk factors and the mediating biological/psychological processes.

After reading this book, if I were to be asked if we are on the verge of a tipping point of a new generation of antidepressants, I would have to answer in the negative. I acknowledge understanding the precise mechanisms of action of antidepressants, is a critical and worthy goal. I also acknowledge that current antidepressants are not perfect and individualized medicine may aid their efficacy. However, I am not convinced that the financial case and theoretical caricature of depressive disorders presented in this book justifies the urgent need for a next generation of antidepressants.

In summary, this book provides a single cohesive view that antidepressant drugs currently in development will bring great benefit; however, this is a view that I would have liked to have seen tempered by better consideration of its limitations.

References

Flint J, Munafo MR (2007). The endophenotype concept in psychiatric genetics. *Psychological Medicine* **37**, 163–180.

LeDoux J (2002). *Synaptic Self: How Our Brains Become Who We Are*. Macmillan: London.

Miller G (2010). Is pharma running out of brainy ideas? *Science* **329**, 502–504.

Pringle A, Browning M, Cowen PJ, Harmer CJ (2010). A cognitive neuropsychological model of antidepressant drug action. *Progress in Neuropsychopharmacology and Biological Psychiatry*. Published online: 29 July 2010. PMID: 20673783.

Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z (2006). Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Archives of General Psychiatry* **63**, 1217–1223.

NICHOLAS D. WALSH, Ph.D.
(Email: nickwalsh100@gmail.com)

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