

Psychopharmacology: From serendipitous discoveries to rationale design, but what next?

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Abstract

Psychopharmacology really developed as a discipline from the mid-20th century with the discovery of a number of new classes of psychoactive drugs which could modify behaviour. These drugs were discovered as a consequence of clinical observations of patients, often being treated for other conditions. These serendipitous discoveries were the start of an era of drug development which has led to the antidepressants, antipsychotics, anxiolytics and mood stabilisers used today. Subsequent research focused on understanding why these drugs were effective, and used this information to develop a second generation of drugs that were more selective for their therapeutic targets, and therefore had reduced side effects and improved safety and tolerability. After a period of decline in new discoveries and withdrawal of the majority of the major pharmaceutical companies from active development programmes in psychiatry, new avenues are emerging fuelling renewed interest in this area.

Keywords

Psychiatry, antidepressants, antipsychotics, animal models, behaviour

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Introduction

Psychopharmacology has seen huge advances in the last 50 years with the majority of currently licenced psychotropic drugs being developed since the 1950s. The era of contemporary psychopharmacology started with the discovery of a number of novel compounds which could specifically modify human behaviour (Carlsson, 1990; Hyman, 2013; Lopez-Munoz et al., 2012; Shorter, 2008). Throughout human history, there is evidence of people using psychoactive substances to alter their behaviour (Crocq, 2007; Moriarty et al., 1984). These drugs were most commonly used for their mind-altering effects or ability to induce feelings of pleasure. The hypnotic effects of different drugs have been understood by humanity throughout history with drugs such as alcohol and the opiates well known for their anxiolytic and sedative effects. In the late 19th century and into the early 20th century, drugs such as paraldehyde, chloral hydrate and bromides were being used as treatments for anxiety disorders; however, it was the discovery of the barbiturates in the early 20th century which probably saw the start of the development of psychopharmacology.

As illustrated in Figure 1, the development of drugs to treat specific psychiatric disorders really began in the 20th century. It is interesting to note, however, that the origins of all the major classes of drugs used to treat psychiatric disorders stem from clinical observations made when investigating treatments for usually unrelated conditions. In 1937, Dr Charles Bradley reported the beneficial effects of benzedrine (racemic

amphetamine) in what we now describe as attention deficit hyperactivity disorder (ADHD). The drug was being given to children for severe headaches and Bradley observed that it improved their behaviour and school performance. This was the start of a long history of the use of stimulant drugs to treat ADHD (Mayes and Rafalovich, 2007). In 1949, John Cade worked out that lithium salts could cause sedation in guinea pigs and rapidly moved onto testing lithium in patients with mania. Advances in organic chemistry also facilitated the production of a wide range of novel compounds which were tested for their potential clinical use. The primary interest at that time was in the development of new anti-microbials, anti-parasitics or drugs which could be used to induce sedation or anaesthesia rather than treat psychiatric disorders. Newly synthesised compounds were then tested on animals to assess their effects and safety. The relatively limited legislation compared to today's standards meant that many of these compounds progressed quickly into tests in human patients. As clinicians observed the effects of these drugs, they noted that some changed mood and behaviour. It is these early serendipitous

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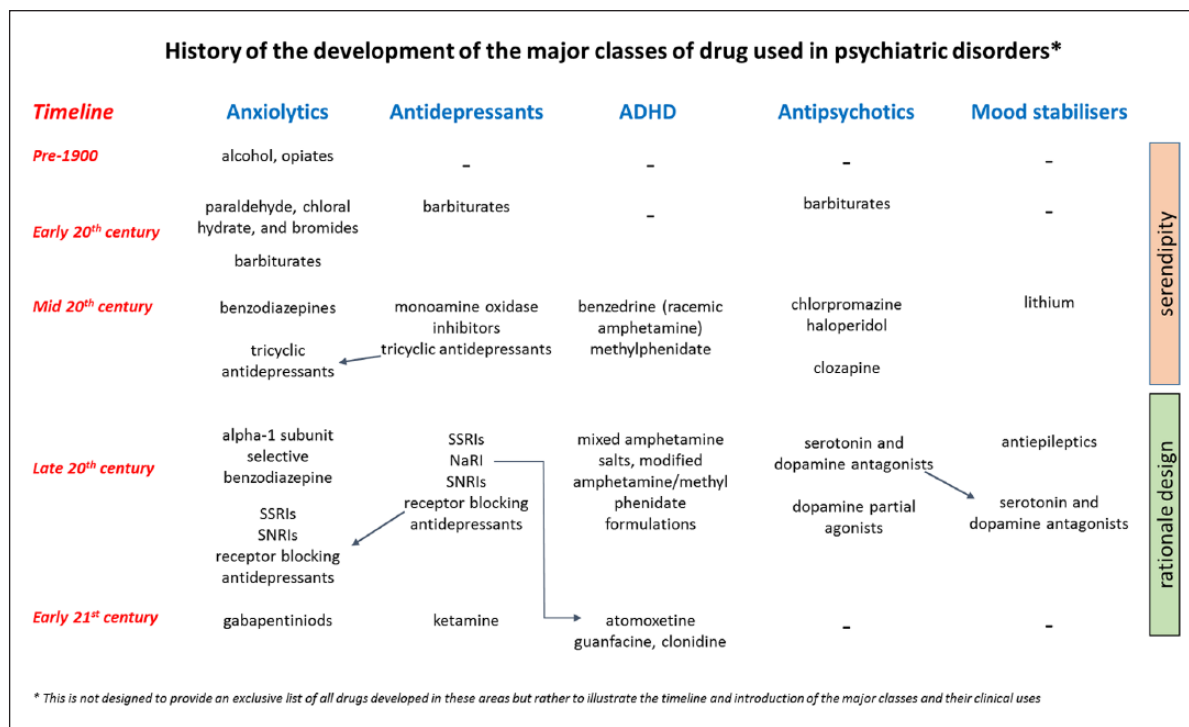


Figure 1. Drugs have been used to modify behaviour throughout humanity; however, the clinical use of drugs for specific conditions really developed from the start of the 20th century. This overview illustrates the timeline associated with the major classes of drugs used to treat psychiatric disorders. Although defined by their therapeutic target, the figure also indicates (arrows) where the same drugs have multiple therapeutic indications. An alternative approach to classification of psychiatric drugs is based on their psychopharmacology. Referred to as 'Neuroscience-Based Nomenclature' (<http://www.nbn2.com/>), this initiative has recategorised these drug treatments based on their pharmacology and mode of action rather than their first therapeutic indication.

discoveries which underpin all the major classes of drugs used in psychiatry today. The following chapter considers the role serendipity played in the discovery of the major types of treatment used in psychiatry today. There is a brief overview of all the major drug classes and then a more detailed discussion relating to the anxiolytics, antidepressants and antipsychotics. In relation to these classes of drugs, this article considers how psychopharmacology helped to unravel their biochemical targets and used this knowledge to support the rationale design of improved treatments. The final section looks to the future and considers where the next major developments in the treatment of psychiatric disorders may come from.

Discovery of the major therapeutic classes and their associated pharmacology

The discovery of all the major classes of psychoactive drugs used in psychiatry today preceded a detailed knowledge of their biochemical targets or mechanisms of action. The drugs also came into widespread clinical use at a time when very little was known about the biological basis of these behavioural disorders. In many ways, the discovery of these drugs has also provided the greatest insights into the relationship between chemical processes in the brain and behaviour. However, even today, our understanding of the causes of psychiatric disorders is limited

and many patients fail to respond to current treatment. Technological advances over the last 50 years have enabled progress in our knowledge of the biochemical targets of psychoactive drugs, facilitating a rationale design strategy to refine their therapeutic effects while reducing side effects and improving safety and tolerability. The development of methods to characterise the receptor binding profile and intrinsic activity of these compounds, as well as their behavioural effects in rodent models (see Box 1), was critical in this process. In many cases, it is this knowledge that has facilitated the development of the next generation agents, which in themselves have helped further our understanding of their mechanisms of action. Although rationale design has played a key role in the design and development of these new treatments, many have ended up with licences for indications in addition to, or instead of, their initial therapeutic target. For example, atomoxetine is a noradrenaline reuptake inhibitor that was initially evaluated as an antidepressant but is now licenced for the treatment of ADHD providing an important alternative to stimulant medications. It should also be noted that psychopharmacology is still broadly divided into drug classes based on their main therapeutic target despite the fact that many of the drugs used in psychiatry may be licenced for and used in different conditions (see Figure 1 and the neuroscience-based nomenclature, <http://www.nbn2.com/>). This is further illustrated for anxiolytics, antidepressants and antipsychotics in the following sections. Treatments for ADHD and bipolar disorder are summarised in Figure 1 but are not discussed in detail.

Role of animal models in psychopharmacology

Arguably one of the most important methods in the history of psychopharmacology has been animal models. During the era of early drug development, animal studies played a crucial role in evaluating the effects of drugs of unknown pharmacology. A screen through a range of animal tests could detect simple behavioural effects such as sedation, anticonvulsant properties and muscle relaxation. Although somewhat crude by today's standards, these animal studies were critical in identifying safe drugs and providing an evidence base from which to build a clinical study.

Following the serendipitous discovery of a range of psychotropic drugs, the next phase of drug development, rationale design, required more sophisticated methods. The availability of clinically effective treatments for a range of diseases were used to develop and validate new animal tests which could predict clinical efficacy. The key requirement for these animal models was selectivity whereby only drugs with specific properties would show efficacy. Good examples of these models are the forced swim test and pre-pulse inhibition used to assess potential antidepressants and antipsychotics respectively. The development of these tests would not have been possible without the clinically effective drugs to use to validate them. It was not necessarily the focus of the development of these models to recapitulate the disease itself but more about predictive validity. These tests have played an important role in the development of the second generation drugs with improved safety and side effect profiles. Whilst often criticised by today's standards, methods such as the forced swim test, PPI and PCP- or amphetamine-induced hyperactivity have been invaluable in terms of the development of many of the drugs currently used in psychiatry.

The challenges facing researchers today are different and it is now widely acknowledged that these animal models are no longer suitable for the types of drug discovery programmes needed to move forward to a third generation of treatments. Their major downfall is that they lack translational validity. In order to identify novel drug targets rather than refining the drugs from similar classes, methods in animals need to better recapitulate characteristics of the human condition. This is not an easy challenge to address when you consider that all current methods to assess and diagnose psychiatric disorders use subjective, self-report measures, something animal researchers can never accomplish. The answer perhaps lies in approaching both the clinical and the pre-clinical methods used to assess psychiatric symptoms and the development of more objective methods in the clinic which can translate to animal studies (see final discussion and box 2 for example).

Box 1. Role of animal models in psychopharmacology.

Anxiolytics

Probably the disorder for which humans have longest sought 'treatment' is anxiety with alcohol and opiates used to induce feelings of relaxation and calm. The origin of anxiolytic drugs was the barbiturates which were first synthesised in the early 20th century with diethyl-barbituric acid introduced for clinical use in 1904. The drug was the start of a new era of treatment for a wide range of psychiatric conditions and was also the first effective treatment for epilepsy. Acting through the GABA_A (gamma-aminobutyric acid) receptor, this positive allosteric modulator could potentiate the effects of endogenous GABA to induce sedative and hypnotic effects making it an effective treatment for a range of psychiatric disorders. Patients with severe neuroses or psychoses were sometimes administered intravenous barbiturates which enabled them to benefit from psychotherapy (Lambert and Rees, 1944). It is interesting to consider how this may relate to the recent use of intravenous ketamine in treatment-resistant depression and the revisiting of the use of psychedelics in the treatment of a number of the more severe psychiatric disorders. The barbiturates enjoyed a long period of use with little competition, but the development of the safer benzodiazepines saw their use for anxiety and sleep disorders rapidly decline. The first benzodiazepine chlordiazepoxide was discovered serendipitously, but its potential to provide a safer alternative to the barbiturates saw Hoffmann-La Roche rapidly bringing it to market with structural analogues such as diazepam following closely behind (Wick, 2013). The rapid onset of action of their anxiolytic effects makes the benzodiazepines very useful for short-term

management of anxiety-related disorders but they are also associated with dependence and tolerance and so their long-term use is restricted.

Both the barbiturates and benzodiazepines act through enhancing inhibitory transmission via the GABA_A receptor but these receptors are widespread throughout the brain and are involved in many different functional roles. Attempts to develop more selective anxiolytics have principally followed two avenues. The first sought to apply a rationale design approach to identify and target GABA_A receptor subunits which were involved in the modulation of anxiety but not sedation, muscle relaxation, or tolerance and dependence. The second was to identify novel mechanisms linked to the pathophysiology and target specific receptors which were identified as playing a role in anxiety-related behaviour.

The efficacy of the barbiturates and benzodiazepines and a more detailed understanding of the complexity of the GABA_A receptor fuelled studies to try to develop more selective compounds. As molecular methods improved, evidence for many different subunits and subunit combinations associated with the GABA receptor complex became apparent. Extensive characterisation of these is still ongoing and beyond the scope of this discussion but may well deliver better anxiolytics in the future. Alpha1 subunit selective compounds have been developed on the basis that they would have lower abuse liability and drugs such as zolpidem show some preference in binding for the alpha1 subunit. They also have a short half-life and are generally only used as hypnotics although they do have anxiolytic properties.

Among the other targets, the serotonin system has been the most successful in terms of new treatments for anxiety and much

of this has occurred alongside the development of the second-generation antidepressants (discussed in the next section). Serotonin is implicated in anxiety as well as major depression (Andrews et al., 2015; Deakin, 1998) although the exact role of this system in the aetiology of these conditions is not fully understood. Two of the many serotonin receptor subtypes found in the brain seem to be particularly important in affective processing: the 5-HT_{1A} and 5-HT_{2A} receptors (Carhart-Harris and Nutt, 2017). Two major groups of serotonergic anxiolytics have been developed: the azapirones which are 5-HT_{1A} partial agonists and also enhance dopaminergic and noradrenergic function (Eison and Temple, 1986), and the serotonin-specific reuptake inhibitors (Nutt et al., 1999). Both of these drug classes offer a non-sedating anxiolytic without the risk for dependence and abuse. The azapirones have shown efficacy for generalised anxiety and buspirone has been used as an adjunct therapy in major depression although their clinical success has been limited and they are not widely prescribed today. As a detailed understanding of how 5-HT and its complex family of receptors interact with anxiety disorders is still not fully understood, the reasons why these drugs have failed to deliver is still not understood. One theory relates to the location of the 5-HT_{1A} receptor and the fact that it is found in a post-synaptic location where agonism has a therapeutic effect but it is also a pre-synaptic autoreceptor where activation leads to reduced endogenous serotonin release. Although the azapirones are not widely used in the clinic and have largely been superseded by the selective serotonin reuptake inhibitors (SSRIs), it is interesting to note that the antipsychotic clozapine and two new antidepressants, vilazodone and vortioxetine, include partial 5-HT_{1A} receptor agonism alongside their other pharmacological effects (Köhler et al., 2016). The SSRIs in contrast have rapidly become the first-line treatment for generalised anxiety disorder (Baldwin et al., 2014). Acting through inhibition of the serotonin transporter, these drugs alongside the mixed serotonin and noradrenaline reuptake inhibitors have shown efficacy in a variety of anxiety disorders. Unlike the drugs acting through the GABAergic system, their effects are non-sedating but also improve with time and clinical benefits are often delayed with a period of time needed between initially taking the medication and subjective changes in the patient's perception of their symptoms (see further discussion below). The reasons for this are not yet fully understood with different hypotheses proposed including receptor adaptation, specifically with regard to the 5-HT_{1A} and 5-HT_{2A} receptor subtypes.

The final group of drugs which has recently become more widely used in the treatment of anxiety is the calcium channel modulating gabapentinoids of which pregabalin is the most commonly prescribed treatment for anxiety (Baldwin et al., 2013, 2014). Originally developed for the treatment of epilepsy and thought to be acting through a GABAergic mechanism, gabapentin and pregabalin are known to be anxiolytic with reduced adverse side effects compared to the SSRIs, for example, sexual dysfunction. However, evidence of their abuse liability and risks associated with co-administration with other drugs of abuse are a concern (Baldwin et al., 2013; Lyndon et al., 2017).

Antidepressants

Antidepressant effects of drugs were first seen unexpectedly in patients being treated for very different, non-psychiatric conditions.

Among these, the first mood-improving drug was iproniazid, which was first used to treat tuberculosis (Berger and Barchas, 1977). The tricyclic antidepressants (TCAs) originate from the initial observations that chlorpromazine was an effective treatment for psychiatric patients, inducing a distinct type of sedation. Chemists seeking to develop related compounds synthesised the first antidepressant, imipramine, which was trialled in 1955 (Kuhn, 1958). Interestingly, its effects were observed after only a few days which appear somewhat in contradiction with our current view of the delayed onset of action of conventional antidepressants (Kuhn, 1958). Subsequent pharmacological studies revealed that both iproniazid and imipramine were able to increase monoamine transmitter levels in the brain through distinct mechanisms; iproniazid acting via inhibition of monoamine oxidase and imipramine acting via monoamine (noradrenaline and serotonin) reuptake inhibition (Axelrod, 1972; López-Muñoz and Alamo, 2009; Slattery et al., 2004). Over a similar era, the pharmacology of other drugs which affected mood was also pointing towards a central role for the monoamine transmitters – particularly noradrenaline and serotonin. For example, the antihypertensive drug, reserpine, was found to cause depression in patients which was attributed to its ability to deplete monoamine levels in the brain (Freis, 1954). This evidence was central to the monoamine hypothesis of depression, which proposes that depression arises due to a deficit in monoamine function and triggered a surge in interest in developing a second generation of antidepressant drugs (Heninger et al., 1996; Nutt, 2008; Schildkraut, 1965). The aim for chemists and pharmacologists was to develop novel drugs which could mimic the monoamine transmission-enhancing effects of first-generation antidepressants, but reduce the side-effect burden which arose from the extensive receptor-binding profiles of these early antidepressants. Perhaps, the most important development needed was an improvement in safety. The TCAs have a low therapeutic index meaning overdose is a major risk in this vulnerable population. The early irreversible monoamine oxidase inhibitors also suffered from drug and food interactions. In the 1990s, the rationally designed selective serotonin and/or noradrenaline reuptake inhibitors reached the market and have subsequently become some of the most widely prescribed drugs in the world (Cleare et al., 2015). Targeting the reuptake transporter selectively had achieved the initial objective of maintaining the effectiveness of the TCAs but with reduced side effects and improved safety and tolerability. As discussed previously, these drugs are now also the most common treatment for many anxiety disorders (Nutt et al., 1999).

The SSRIs and subsequent family of second-generation antidepressants have certainly improved the treatment of depression but they are not without side effects. Initial increases in anxiety, emotional blunting, gastrointestinal (GI) disturbance and sexual dysfunction are all linked to their effects on serotonin levels in the central nervous system (CNS) and periphery and while some do improve with time, there is still room for further improvements. Attempts to reduce these side effects, improve effectiveness and address concerns over the delayed onset of action have also led to a small number of newer antidepressants reaching the market (Carvalho et al., 2016). These have largely been drugs where multiple sites of action have been attributed to their clinical benefit, for example, multiple therapeutic mechanisms. For example, mirtazapine is a receptor-blocking antidepressant which blocks alpha-2 adrenoceptors, 5-HT₂ and 5-HT₃ receptors

(Stimmel et al., 1997). This combination of pharmacological targets produces a more sophisticated neurochemical alteration. Alpha-2 adrenoceptor antagonism results in increased synaptic levels of both noradrenaline and serotonin, while the blockade of the 5-HT₂ and 3 receptors helps to moderate some of the known 5-HT-mediated side effects and has the potential to enhance efficacy (Nutt, 1998; Stimmel et al., 1997). Agomelatine deviates from the more typical monoamine targets but is a 5-HT_{2C} antagonist alongside agonism at the melatonin receptors and therefore has less of the serotonergic side effects and is reported to have reduced emotional blunting (Carvalho et al., 2016; De Berardis et al., 2011). Other new antidepressants with mixed receptor and reuptake actions are vilazodone and vortioxetine (Köhler et al., 2016) which include 5-HT_{1A} partial agonism.

The latest development in antidepressant therapy has been the use of intravenous infusions of low, sub-anaesthetic doses of ketamine (Machado-Vieira et al., 2009; Zarate et al., 2006). Exhibiting a very rapid and relatively long-lasting antidepressant effect, this non-competitive N-methyl-D-aspartate (NMDA) antagonist has further complicated the picture in terms of how antidepressants work but also sets the challenge to researchers to find similarly effective treatments but lacking the adverse effects associated with ketamine. There is also renewed interest in the use of psychedelics in the treatment of mood disorders (Carhart-Harris and Nutt, 2017) including new evidence about the effects of drugs such as the 5-HT_{2A} agonist, psilocybin on brain activity in relevant regions (Carhart-Harris et al., 2017) and on emotional processing (Stroud et al., 2018). The serotonin releasing agent, 3,4-methylenedioxymethamphetamine (MDMA), has also been shown to modify emotional processing and affect brain activity in regions linked to major depressive disorder (MDD) suggesting it may be effective as an antidepressant (Carhart-Harris et al., 2014).

Many attempts to explain the actions of antidepressant drugs have been made but these still remain hypotheses, with basic research and clinical evidence both for and against. A lack of good biomarkers, or robust evidence for causality in humans, coupled with the limitations of animal models (see Box 1), makes the challenges of understanding the neurobiology of depression all the more difficult. Another key question comes in the mismatch between the rapid onset of biochemical changes induced by antidepressants and the much slower rate of onset of clinical efficacy. Attempts to explain this temporal inconsistency and to use this knowledge to develop new treatments have so far been largely unsuccessful. Hypotheses relating to receptor adaptation (Artigas et al., 1996; Blier, 2001; Charney et al., 1981), neurotrophic effects (Duman and Li, 2012; Duman et al., 1999; Sahay and Hen, 2007) and neuropsychological mechanisms (Harmer et al., 2017; Robinson and Roiser, 2016) have all been proposed and significant bodies of both clinical and preclinical evidence have been reported in their support. However, it remains unclear why people get depressed or how antidepressant drugs work to alleviate these symptoms making the generation of new antidepressants a challenge.

Antipsychotics

The first antipsychotic discovered was chlorpromazine which was noted for its ability to induce a calming effect that was distinct from the sedation seen with the barbiturate drugs (Courvoisier,

1956; López-Muñoz et al., 2005). Soon after the discovery of chlorpromazine, Paul Janssen and colleagues observed that a butyrophenone compound they had synthesised had similar effects in animal studies to chlorpromazine but was less potent (Granger and Albu, 2005; Janssen et al., 1960). Clinical trials of this new drug, haloperidol, found it to be very effective against the hallucinations and delusions in psychosis (Divry et al., 1958). These drugs were the foundation for the typical antipsychotics, with around 40 different compounds licenced between 1950 and 1975 (Shen, 1999). Similar to the story for the antidepressants, little was known about the mechanism of action of these drugs or why they were able to alleviate positive symptoms. Later studies, however, suggested that the efficacy of antipsychotics was related to their binding at D₂ receptors (Seeman et al., 1976). Perhaps, one of the most redrawn figures in psychopharmacology textbooks, the correlation between affinity for the D₂ receptor and clinical efficacy, has been a major factor in support for the dopamine hypothesis in schizophrenia (Seeman et al., 1976). Despite the ability of these drugs to provide powerful effects on behaviour and to modify psychotic symptoms, their actions were not specific. Side effects associated with dopamine receptor blockade in the nigrostriatal pathway, hormone effects and binding at other receptor sites led to a heavy side-effect burden.

The side-effect burden faced by patients treated with these antipsychotics was a concern, primarily arising from hormonal and extrapyramidal side effects, and there was a clear need for more effective treatments. However, it was not until 1990 that a new atypical antipsychotic was introduced. Clozapine had first been discovered in the 1950s when a researcher was synthesising derivatives of the antidepressant imipramine (Schmutz and Eichenberger, 1982). Early trials suggested an antipsychotic action but clozapine also caused agranulocytosis and the death of some patients, leading to its withdrawal from use (Griffith and Saameli, 1975; Gross and Langner, 1966). Clozapine was reintroduced in the 1990s following studies which showed that it had lower incidence of extrapyramidal side effects and was effective in some treatment-resistant populations (Kane et al., 1988). This was the start of a new era in antipsychotic treatment with a number of new drugs coming to the market which all shared a reduced propensity for extrapyramidal side effects. The range of pharmacological effects of the atypical antipsychotics is diverse although the majority exhibit high affinity for the 5-HT_{2A} receptor and are sometimes referred to as dopamine and serotonin antagonists (Kim et al., 2009; Seeman, 1990). There are also newer agents such as aripiprazole which are partial agonists at D₂ receptors as well as 5-HT₂ receptor antagonists. Although sharing some pharmacological characteristics, the atypical antipsychotics are a relatively diverse class of agents and linking their specific biochemical targets to their behavioural effects remains a challenge (Kim et al., 2009). The main difference between the typical and atypical drugs is their likelihood of inducing extrapyramidal side effects. Research suggests that this may involve the combined actions at serotonin and dopamine receptors. It may also relate to more favourable pharmacokinetic profiles, making it easier to maintain an antipsychotic dose while avoiding motor side effects.

While these atypical antipsychotics have in the same way as the second-generation antidepressants led to improvements in patient care through reduced side effects, the overall efficacy of these compounds is not really improved (except perhaps clozapine).

Meta-analyses have overall failed to find good evidence supporting improved efficacy for alleviation of negative or cognitive symptoms although a lower side-effect burden has reduced the adverse effects of treatment of these other symptoms in schizophrenia. Attempts to develop drugs to target the negative symptoms have not as yet delivered new treatments, and patient's cognitive symptoms remain unresolved. Emotional aspects of the disease can be treated with additional therapies such as antidepressants but essentially, antipsychotic drugs are primarily a method for managing psychotic symptoms and neither address the whole spectrum of the disease nor treat the underlying cause.

As with the antidepressants, many attempts to explain the relationship between effective treatments and underlying disease biology have been made; however, the cause of schizophrenia remains unknown. Knowledge of the receptor-binding profiles and neurochemical effects of the antipsychotics supported a key role for dopamine receptors (particularly D2) and the hypothesis that schizophrenia is a disease of hyperdopaminergic function developed (Horacek et al., 2006; Moncrieff, 2009). Both animal studies and observations in patients have shown that drugs which elevate dopamine levels in the brain can induce, in normal subjects, the positive symptoms of schizophrenia (Lieberman et al., 1990). Similarly, drugs acting at the 5-HT_{2A} or NMDA receptor have a similar propensity to induce positive symptoms which in animals can be attenuated by pre-treatment with antipsychotics (Halberstadt and Geyer, 2013; Jones et al., 2011; Steinpreis, 1996). Despite this large body of pharmacological evidence, studies in patients are less clear with few studies finding any robust evidence of neurochemical deficits which could explain why these drugs are effective. In recent years, there has been a shift towards the idea that schizophrenia is a developmental disorder which manifests in adolescence when the 'damage' starts to have profound effects on the patient's behaviour. Birth cohort studies have found that there are early signs of impairment in patients who go on to develop schizophrenia, and these can be detected as early as the 1-year developmental milestones (Isohanni et al., 2001). There is also increasing evidence that early cognitive and emotional impairments develop before the onset of psychoses and these represent an important new area to try to target in terms of alleviating symptoms and potentially preventing or delaying the onset of positive symptoms (Jahshan et al., 2010). Although some trials have been completed, to date, no successful drug treatment for the cognitive impairments in schizophrenia has reached the market.

Where next?

The last 50 years have seen huge advances in the field of psychopharmacology; however, there remain a lot of unknowns relating to the cause and treatment of psychiatric disorders. As discussed in the examples above, the refinement of the pharmacological targets has aided the development of more specific and thus better tolerated drug treatments and the benefit of this in terms of patient care should not be underestimated. Animal models have also played a major role in the clinical progression of these treatments though there are notable caveats to this research strategy (see discussion Box 1). The challenge for the next 50 years is to more precisely define the relationships between these biochemical targets and effects on behaviour. Moreover, the underlying pathological processes which lead to the disease and how current therapies interact with these processes remain to be fully elucidated. Because of this

lack of knowledge, we do not know whether current treatments intervene with the underlying neurobiological mechanisms of psychiatric disorders directly, indirectly or actually target more downstream processes that are merely linked to these abnormal behaviours. New treatments are clearly needed as many patients fail to respond to current drugs or retain residual symptoms. Side effects of these drugs, even the newer second-generation ones, are still an issue and for most patients, long-term medications are needed with relapse common. For many patients, the conditions are lifelong with current treatments providing a means to manage symptoms but are not a cure.

So, what does the future for psychopharmacology look like? Box 2 provides a summary of some of the areas I consider may have the biggest influence on the future of psychopharmacology, how we consider psychiatric disorders and approaches to their treatment.

One area which offered great promise and potentially a route to new treatments was the role of genetics in psychiatry. However, despite the huge volume of research in this area, it has proved to be a complex field with many genes linked to vulnerability but with varying degrees of penetrance. Knowledge around genetics and the ability to generate genetically modified animals are now widely used to generate disease models and evaluate novel drug targets, but how well these recapitulate the human condition is difficult to quantify considering the limitations associated with methods to quantify the arising behavioural phenotypes (see Box 1). There is also increasing evidence of the complexity of understanding how these genes interact with environmental factors and the role epigenetic mechanisms play in the relationship between genetic risk and manifestation of disease (Mahgoub and Monteggia, 2013). These epigenetic mechanisms may in themselves provide new targets for intervention. Although yet to deliver new targets, the identification of mutations which are associated with increased risk could also yield new opportunities for research and development as a greater understanding of the associated pathways and relationship to pathophysiology develop. For example, stem cells derived from patients could be used to generate cell lines to study the specific impact of the mutation on neurobiology (Wen, 2017). Using genetic information to define subpopulations within the core diagnoses may also provide a route to better diagnosis and targeting of the most suitable medication. Studying the neurobiology of psychiatric disorders has also extended beyond the brain with evidence for a central role for the immune system (Dantzer et al., 2008; Horowitz et al., 2013; Khandaker et al., 2014; Mondelli et al., 2017) and most recently ideas relating to the microbiome and how the gut-brain interactions may contribute to mental health (Clapp et al., 2017; Rea et al., 2016).

Methods to study the brain in relation to mental health have also seen major advances. For example, optogenetics and chemogenetics provide research tools to selectively target distinct neuronal populations and pathways to enable investigations into their role in behaviour (Kim et al., 2017; Sjulson et al., 2016; Steinberg et al., 2015; Urban and Roth, 2015). While currently a research tool, there is the potential for future treatments to build on these methods whereby the restrictions associated with current drug treatments, that is, they hit all receptors expressed within both target and non-target regions, could be addressed (Whittle et al., 2014). Could the future of psychopharmacology include the use of viral-mediated gene transfer of novel, designer receptors or optically activated receptors which can then be used

Examples of some of the new methods and areas of development relevant to the future of psychopharmacology

1. Genetics and epigenetics: The sequencing of the human genome has made it possible to study genetic risk and disease in a way never previously possible. Population level studies have been used to identify genetic risk factors associated with psychiatric disorders but their relationship with disease is complex. Some rare gene mutations carry very high risk but are not 100% associated with disease meaning that other, environmental factors are involved. There are also a very large number of low risk genetic mutations which occur at much greater frequency but have a much lower risk of causing disease. Genetic studies have not yet been able to unlock the pathophysiology of mental health conditions or provide new drug targets. The complexity of the relationship between genes and the environment suggest that it is unlikely to be something which will be understood soon. One exciting prospect though is the potential to use genetic information to stratify patient populations including using genetic factors to understand drug responses to help optimise treatments in the future.

The epigenome is a product of the individual's environment which promotes adaptive behaviour through modifying how DNA is translated. The process involves histone acetylation and deacetylation, and DNA methylation, which produce lasting and stable changes in gene expression. In psychiatry, these epigenetic changes are thought to underlie the interaction between genetic risk or resilience and environmental factors. They can help explain why environmental influences such as neurodevelopmental insults, early life adversity and stress increase the risks for developing a mental health condition. Whilst an evolutionary strategy which promotes adaptability in an unstable environment, epigenetics may also hold the key to how genetic risk and the environment together lead to mental health conditions. As the details of these more complex gene x environment interactions are understood, the potential to interact with these processes using novel drug treatments may become feasible.

3. Beyond the brain: There is increasing awareness that the brain and mental health conditions are not necessarily just a disease involving the central nervous system and that the immune system may play an important role. For example, estimates suggest that 30-40% of patients with major depression have elevated levels of inflammatory markers in their blood which may arise because of the bodies response to chronic stress. This activated immune system may mediate the detrimental effects of stress in the brain including effecting processes such as neurogenesis and synaptogenesis. The link between immune activation and inflammation in major depression is evident in patients treated for hepatitis C using interferon-alpha where at least 50% may develop depression during treatment. For decades, Schizophrenia has also been linked to immune activation particularly in relation to maternal exposure to infections agents. Supported by animal studies it seems that the immune response triggered by these infections can have neurodevelopmental effects which increases the risk of schizophrenia in the offspring. More recently, genetic studies have revealed risk factors associated with genes linked to immune modulation.

Another interesting development has been our awareness and knowledge of the microflora in the gut, or microbiota, and its interactions with inflammation, the immune system and nervous system. Disturbances to the composition and the diversity of the microbiota has been linked to a variety of diseases and most recently mental health conditions. Knowledge about the bidirectional communication between the gut and the brain, 'the gut-brain axis' and its relationship with the immune system is still in its infancy but inflammation in the gut and disturbances to the normal balance of gut flora has been linked to mental health conditions, particularly anxiety and depression. This raises the exciting prospect of a new approach to treatment through targeting gut health. Current interest is focused on understanding the microbiome, the genetic make-up of an individual's microbiota, and relating this to their mental health. Treatments can then be targeted on modifying the microbiome through approaches such as probiotics.

4. Advances in methods to study the brain: Technological advances have revolutionised the way we study brain function in humans and in animals. Improvements in computational methods have allowed much larger quantities of data to be generated and analysed and now extend to the ability to create computational models of neuronal circuits. This technology is behind many of the advances in brain imaging as well as electrophysiological methods to record the activity of individual neurones, circuits and populations. With each advance in technology the temporal and spatial resolution improve and our ability to understand how the brain works increases.

One of the biggest advances for fundamental biology has been the development of optogenetic and chemogenetic methods to manipulate the function of specific neuronal populations or pathways. Using viral-mediated gene transfer in combination with cell-type specific promoters or specific types of genetically modified animal, optically activated ion channels or designer receptors can be expressed within the region or circuit of interest. These can then be controlled by the experimenter using either light or exogenously administered drugs and the specific function of the region of interest studied. In psychopharmacology, studies have always been limited by the drug affecting either the whole brain (following systemic

(Continued)

Box 2. (Continued)

administration) or restricted to targeted drug infusions which still influence all cell types in the region. This method provides a route to achieving much greater specificity thus enabling studies into the role of specific drug targets within a defined population. Currently this is limited to a research tool, but could this be the future for psychopharmacology? The targeting of designer drugs to dysfunctional neuronal populations or circuits to enable much greater specificity and reduced side effects?

5. Biomarkers and objective methods to quantify disease: To my mind, one of the biggest challenges in mental health and psychopharmacology is the way which diseases are diagnosed and severity and response to treatment are quantified. The reliance on subjective, self-report measures using clinical interviews and questionnaires makes it difficult to fully categorise the diversity which exists in the symptoms experienced by patients. It also potentially limits sensitivity when quantifying response to treatment for example during clinical trials. A further very significant issue relates to animal studies where it is impossible to directly translate between psychiatric symptoms in patients and behavioural measures used in pre-clinical studies. An obvious way to address this would be through the validation of objective biomarkers however, identifying a simple blood-based measure has not proved feasible for any psychiatric disorder. Although imaging methods have provided some potential neural signatures associated with disease, these are not cost-effective for large scale trials or diagnosis and have not yet proved to be sufficiently reliable or sensitive as a diagnostic test. An alternative approach may be to use cognitive biomarkers. Neuropsychological tests can provide an objective measure of deficits in specific cognitive domains which also represent important targets for therapeutic intervention and hence studying response to treatment. They can also provide a route for the development of better, translational animal models which could improve studies into fundamental biology and pre-clinical psychopharmacology.

Box 2. Examples of some of the new methods and areas of development relevant to the future of psychopharmacology.

to manipulate the activity of a specific, dysfunctional pathway? Both fundamental biology research and clinical studies have benefitted from advances in how the physiology of the living brain can be measured particularly using imaging or electrophysiological methods. Studies recorded from populations of neurones and network activity quantified using electroencephalogram (EEG) or imaging methods are revealing how local and brain-wide networks interact and the dysfunctional activity which is associated with psychiatric disorders. One important aspect on the interpretation of these data is how they relate to deficits at a functional, particularly behavioural, level. These methods are most useful when integrated with behavioural methods but equally, particularly in animal studies, can be limited where the behavioural methods and models have poor construct validity.

Perhaps one of the most important areas for development is the need for robust translational biomarkers which can provide objective methods for diagnosis and to assess response to treatment (Jentsch et al., 2015; Slaney et al., 2018; Strawbridge et al., 2017). Biomarkers could also help with the current challenge of diagnosis and patient stratification. While psychiatric disorders are categorised based on symptom clusters, the current methods, as discussed in the *Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-V)*, do not allow for the heterogeneous nature of many of the conditions. To date, a traditional approach to a biomarker for any psychiatric disorder has failed to provide anything suitable (Jentsch et al., 2015; Slaney et al., 2018; Strawbridge et al., 2017). Perhaps an alternative approach would be to utilise a behavioural approach to these disorders which predominantly manifest as dysfunctional cognitive, emotional and social functioning (Slaney et al., 2018). The Research Domain Criteria (RDoC; Cuthbert and Insel, 2013; Insel, 2014) provides a useful starting point for this approach whereby the different behavioural domains relevant to psychiatric disorders have been described within a framework which includes specific neuropsychological tests and animal paradigms which can provide a quantitative

approach to measuring deficits. Extending this to a more objective, phenotype assessment of how these domains are specifically altered in different conditions has the potential to provide an objective and translatable approach for future psychopharmacological studies. Whether future diagnoses of psychiatric disorder could be made on the basis of such cognitive biomarkers remains to be seen. However, if such developments could be made, then future clinical trials could benefit from a more symptom-based objective assessment. Our own research has attempted to develop a translational and objective approach to studying MDD based on these ideas (Robinson, 2018; Slaney et al., 2018).

Studying emotional disorders in animals has proved very challenging and the ability to relate subjective symptoms of low mood, suicidal ideation and even loss of interest in pleasurable activities to methods used in animals is impossible. However, neuropsychological studies have revealed that patients with depression exhibit changes in emotional processing which can be measured using objective tasks (Robinson, 2018; Robinson and Roiser, 2016). These deficits can be linked to relevant neuronal pathways and show robust sensitivity to antidepressant treatment (Harmer et al., 2017; Pringle et al., 2011). Although not directly translatable, the underlying concept that emotional state can bias cognitive processes has the potential to be translated between species if task can be developed in the appropriate domain (Robinson, 2018). The first example of this was reported in *Nature* in 2004 by Harding et al. and demonstrated that rodents' behavioural responses in a decision-making task were influenced by their affective state. There is now a large body of literature demonstrating that similar affective biases can be observed in a variety of species from invertebrates to humans (Hales et al., 2014; Robinson, 2018). Our lab has also developed a task which can detect biases in learning and memory in a simple task of associative learning. In our affective bias test, animals are presented with two independent learning experiences of equal absolute value, but their affective state is modulated before one of the learning sessions (Stuart et al., 2013).

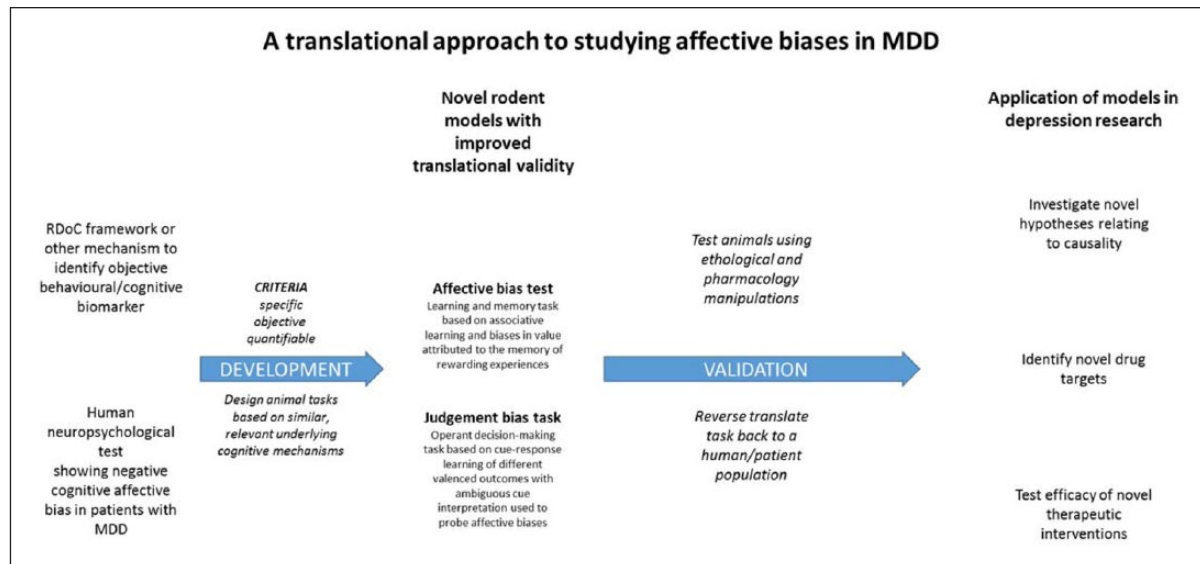


Figure 2. Overview of an approach to develop better translational behavioural methods to study relevant neuropsychological characteristics of psychiatric disorders and improve integration of fundamental biology, preclinical drug discovery and development, and clinical studies. See also discussion in Robinson, 2018 in relation to major depressive disorder.

This leads to a robust bias in the subsequent recall of the value of reward associated with that experience which is consistent with the direction of affective state change, that is, a positive affective state leads to a positive bias and a negative affective state causes a negative bias (Stuart et al., 2013, 2014, 2017). In this task, we observe effects following pharmacological and psychosocial manipulations of affective state as well as effects following acute treatment with antidepressant or pro-depressant treatments which are predicative of their subsequent effects on mood in humans. Furthermore, in the affective bias test, and a modified version of Harding's original decision-making task, we have been able to observe differential effects with conventional delayed onset antidepressants versus the rapid onset antidepressant, ketamine (Hales et al., 2017; Stuart et al., 2015). The actions of these drugs are also linked to relevant neural circuits (Stuart et al., 2015). These data demonstrate how this approach can be used to achieve a more translational approach to studying the psychopharmacology of depression. Could a similar strategy (Figure 2) also be employed for other disorders and behavioural deficits?

In summary, psychopharmacology has seen major advances from the early developments of the major treatment classes used today. Knowledge about the biochemical effects of these serendipitously discovered drugs has been critical to the development of the second generation of treatments which are commonly used today. However, the complexity of psychiatric disorders is becoming more apparent as knowledge about the role of genes and the environment are better understood and there are still a lot of unknowns. While development in understanding of pathophysiology will undoubtedly develop from this knowledge, the challenge for psychopharmacology remains in terms of translating this knowledge into new pharmacological treatments. As such, there may also be a case for not forgetting the past. Novel insights are often gained from very different contexts (i.e. the serendipitous discoveries of 1950s) and perhaps a more blue-skies strategy could bring about novel theories and progress in

our understanding. Better translational methods, including improving animal models, are critical for testing hypotheses from population health, clinical studies and fundamental biology and taking these from the bench, through preclinical development and to the patient.

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