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Transformative technologies in medicine: a primer for psychiatrists

ARTICLE

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SUMMARY

Across medicine, key scientific advances in the past couple of decades have deepened knowledge of fundamental mechanisms of disease, leading to new treatments and the possibility of increased personalisation of care. Some of the most important developments in fields as diverse as immunology, the microbiome, genetics, stem cells and artificial intelligence are summarised in this article to raise awareness among psychiatrists and to help understand the opportunities and challenges they may present for mental healthcare in the future.

LEARNING OUTCOMES

After reading this article you will be able to:

- understand the general concept of 'translational' medicine and the opportunity this presents for 'personalisation' in healthcare
- describe some key clinical advances in fields such as genetics, immunology, stem cells, gut microbiome, neuroimaging, neuromodulation, drug development and information technology
- understand current and possible future application of these technologies in psychiatry.

KEYWORDS

Genetics; other imaging; novel CNS drugs; neuroimmunology; medical technology.

One key way in which progress in medicine in recent decades can be conceptualised is as a shift from descriptive models of disease to a more fundamental understanding of underlying pathological mechanisms. Sequencing of the human genome and wide-ranging molecular technologies have provided an increasingly sophisticated understanding of cellular functioning and, in turn, of disease, particularly genetic disorders and cancers.

'Translational medicine' is a term used to capture the interdisciplinary efforts to 'translate' these basic scientific discoveries into useful clinical advances. For example, identification of genetic abnormalities or altered biological molecules which are biomarkers for a disease potentially allows novel screening/diagnostic techniques or assessment of prognosis and treatment response. Likewise, understanding disease pathways presents new sites for drug action or other therapeutics, such as genetic treatments, stem cells or neuromodulation.

An important aspect of translational medicine is the possibility it provides of a personalised understanding of an individual's disease risk based on their unique genomic sequence, environmental exposure and lifestyle. In turn this allows more tailored advice to be given on prevention and treatment. It is important to recognise that, far from reducing the importance of the environment, personalisation places it at the heart of medicine. 'Personalised' medicine (often called 'precision medicine') has the potential to revolutionise healthcare.

Translational approaches have had profound effects across medicine, particularly in oncology and genetics. Within psychiatry we are at an earlier stage of this journey towards translational medicine and personalisation. We still rely largely on descriptive diagnoses and treatments that are not based on correcting fundamental disease mechanisms. Although in part this sense of being 'behind' other fields could be attributed to the well-documented relative underfunding of mental health research, at the heart of the issue is the fundamental complexity of studying the human brain and the fact that most existing categorical diagnoses capture a wide range of phenotypes.

The aim of this article is to give a non-exhaustive overview of some of the key developments across medicine that are transforming understanding of disease, some of the therapeutics that have resulted from these advances and how they may relate to psychiatry. It is hoped that it will be a useful grounding for psychiatrists, particularly as many of these approaches may have been developed since they attended medical school. Topics covered are summarised in Box 1.

Genetic advances

Epigenetics

Since the landmark completion of the Human Genome Project in 2001 with the sequencing of the entire human genome, we have had the opportunity to refocus our ambitions beyond the linear sequence of DNA and even the three dimensions of higher-level chromatin structure. The study of epigenetics moves us to understand better the

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BOX 1 Key areas of recent biomedical progress

- Genetics – epigenetics, gene editing, messenger RNA (mRNA) therapeutics
- Immunotherapies – cytokines, monoclonal antibodies, cell transfer
- Stem cells
- Gut microbiome
- Neuroimaging
- Neuromodulation – deep brain stimulation, transcranial magnetic and direct current stimulation, vagal nerve stimulation
- New drug treatments
- Information technology – artificial intelligence, brain–computer interfaces

dynamic influences that our genes have on us and our behaviour, and links us right back to the ultimate reason for all our thoughts and actions: our environment.

Epigenetics[a] refers to changes in gene activity or expression that occur without changing the underlying DNA sequence. It is the way that our environment, whether internal or external, and our experiences, whether conscious or subconscious, can affect how our genes work. Some changes can also be passed down from one generation to the next (intergenerational transmission) and epigenetic changes can be particularly influential when they occur at key points in development, as illustrated by the time-dependent nutritional insult in the example below from the Dutch Hunger Winter. The principle epigenetic mechanisms are summarised in Table 1.

Although epigenetic research in humans is still in its infancy, there are examples of how a person's environment or lifestyle can change their genes. The early evidence came from studies of diet and trauma. One way to conceptualise this is that the pattern of expression of our genes is tuned by our early environment and experiences to help us to succeed (or survive) within the continuing conditions of that environment. For example, if we grow up in a world of starvation, we will be epigenetically 'primed' for such a world rather than a world of plenty, or if we are raised in an environment of neglect and fear, we are 'primed' differently than if we are loved and nurtured.

The first suggestion of intergenerational transmission in humans came in a study of Dutch medical records extended longitudinally for several generations after the Dutch Hunger Winter, an acute famine in The Netherlands in 1944–1945.

The study (Lumey 2007) observed that children born to mothers who experienced starvation in the first trimester of pregnancy were of normal birth weight, but later became more vulnerable to obesity and other disorders (including schizophrenia). However, those born to mothers who experienced starvation in the third trimester of pregnancy were small, and remained small for the rest of their lives, but with a low risk of obesity and other disorders.

Furthermore, and unexpectedly, the research identified a persisting effect into the following generation, findings that were replicated in other studies and ultimately linked to transmissible patterns of DNA methylation.

It is important to note that these mechanisms do not work in isolation. There is a complex overlap between gene expression, gene regulation and epigenetic mechanisms, which operate with differing levels of speed, scale and reversibility.

The best examples of environmental factors that influence mental health through epigenetic mechanisms are those of attachment and of trauma/stress. Post-traumatic stress disorder (PTSD) is one of the better understood disorders in terms of the epigenetic processes that may underly the condition, for which there are demonstrated differences in DNA methylation and histone modification of genes associated with the stress response (Klengel 2013; Meaney 2018).

a. Readers may also find it helpful to refer to the article in *Advances* by Lindsey Mizen: 'Demystifying genetic jargon in psychiatry' (Mizen 2023).

TABLE 1 Epigenetic mechanisms

Epigenetic mechanism	Molecular process(es)	Impact on gene expression
DNA methylation	Methyl group added at sites where a cytosine nucleotide is followed by a guanine nucleotide (CpG)	Typically, repression of gene expression. CpG sites are often found in regulatory regions of genes
Histone modification	Changes to the structure of histone proteins around which DNA is wrapped	Can increase or decrease gene expression according to the types of modification, which in turn (and in combination) can influence coiling or uncoiling of DNA to allow or prevent access for transcriptional machinery
Non-coding RNA regulation	sRNAs, microRNAs, long RNAs, circular RNAs	Interaction or interference with mRNA to affect its stability or expression

sRNAs, small RNAs; mRNA, messenger RNA.

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How can epigenetic changes be promoted or reversed in the treatment of mental illness?

It is early days in terms of considering the potential therapeutic approaches, but several strategies are being explored, and these are outlined in Table 2.

Gene editing

Gene editing refers to the process of making precise changes to the DNA sequence. It has been employed, for example, to correct for gene mutations such as those causing sickle cell anaemia (Magrin 2022), haemophilia and certain immune deficiencies through gene therapy, although there are only a handful of licensed gene therapy treatments at this point (Cring 2022). It is also used to help us to study gene function and clearly has the potential to help us to develop new therapies and to interfere with gene regulatory pathways in wide-ranging ways.

It is based on a technology called CRISPR-Cas9, which describes two components: a guide RNA (gRNA), which binds to a target sequence of DNA, and the CAS9 protein, which acts like a pair of molecular scissors to cut the DNA strand at the target site, where the cell's natural DNA repair mechanisms can be used to make specific changes to the sequence.

Although there have been some studies exploring the use of gene editing technology in mental health, particularly for conditions where there is a strong genetic component, such as schizophrenia and depression, this is still a new and experimental area of research and there are no approved gene therapies for any mental disorders. Furthermore, there are significant ethical and safety concerns, particularly about what is regarded as 'normal' and what might be the unforeseen consequences of these approaches.

Implications for psychiatrists

Understanding how epigenetic mechanisms affect human well-being and behaviour not only brings the evolutionary perspective to the fore, but it informs the delivery of holistic care and treatment in the context of a person's life, for example by mitigating or reversing the impact of past experiences. There is some way to go in identifying effective, safe and specific pharmacological interventions that act on such maladaptive epigenetic legacies, but there is both logic and promise in optimising and sustaining positive environmental (including lifestyle) influences, especially at key developmental stages. We (and all living things) live our lives at the interface between our genes and our environment, and it may be helpful to be increasingly mindful in our practice of the epigenetics that is playing out in front of us, and inside us.

RNA therapeutics

The information encoded in the human genome is, in essence, a set of instructions to build the wide array of proteins ('proteome') that are crucial for structural integrity and functioning of the body. Various forms of RNA are critical molecules in the

TABLE 2 Possible epigenetic treatment strategies

Treatment strategy	Action/application	Potential therapeutic use
DNA methyltransferase inhibitors	Block the addition of methyl groups to DNA	Shown to be effective in treating depression and anxiety; an example is azacytidine, which is used in cancer treatment but has significant adverse effects
Histone deacetylase (HDAC) inhibitors	Alter the acetylation status of histones, leading to changes in gene expression	Shown to be effective in treating mental illnesses: a well-known example being valproic acid
Non-coding RNA modulators	Have a range of possible applications and could potentially be used to treat mental illness (see section on RNA therapeutics)	Some have been shown to be dysregulated in several mental illnesses, and sequence-specific molecules might be more narrowly targeted and less prone to wider toxicity
Environmental interventions	'Environmental enrichment' is a type of therapy that seeks to promote positive changes in brain function and behaviour	Studies of epigenetic markers support the premise that neuroplasticity is epigenetically mediated: e.g. children exposed to an enriched environment during their early years had lower levels of DNA methylation in their *BDNF* gene. BDNF is involved in neuronal growth and increased levels are also promoted by exercise (Collins 2020). Many elements of environmental enrichment (e.g. physical exercise, diet, social interactions, exposure to new experiences) have been directly and independently associated with improved mental health outcomes, and there are likely opportunities for such approaches to be individually tailored

BDNF, brain-derived neurotrophic factor.

intermediary cellular steps of transcription and translation. There have been revolutionary increases in understanding of RNA biology in recent decades (Zhu 2022). Using synthetic RNA molecules to modulate these cellular steps, and hence gene expression, is an extremely promising area of new therapeutics, albeit accompanied by challenges regarding delivery into the cell and possible pro-inflammatory effects. Some of the main technologies are listed in Table 3.

Although a recent review (Le Marois 2021) found no current clinical trials of RNA therapeutics within psychiatry to treat mood disorders, a wide range of preclinical studies were described whereby the technologies were being investigated in validated animal models of depression. Taken alongside the more advanced state of research within neurology, including into ways of delivering the treatments to the brain, this supports the hope of future use of RNA technology in psychiatry.

Immunity and immunotherapies

Immunity is the body's ability to recognise and protect against harmful pathogens. There are two main types of immunity: innate (first-line, non-specific defences) and adaptive. Adaptive immunity is acquired following infection, passive (maternal) exposure or artificially (for example through immunisation).

Immunotherapy is the process of treating disease through either activation or suppression of one or more parts of our immune system; this can be general and non-specific or by targeting at a humoral (antibody) or cellular level.

Types of immunotherapy

Non-specific

Cytokines are proteins that are released in response to cellular stresses and serve to coordinate the immune response. Interferons (proteins that alert your body that a pathogen is present) and interleukins (which pass messages between cells) are examples of cytokines. Cytokines are not yet widely used as monotherapies because they are poorly tolerated and have a high risk of severe toxicity. However, they may have a role in combination with other immunotherapies, such as T-cell therapy.

T-cell therapy

T-cell transfer therapy is also known as adoptive cell transfer (or therapy) (ACT), immune cell therapy and adoptive immunotherapy. It involves harvesting an individual's own white blood cells, identifying and reproducing the required cells in a laboratory (over 2–8 weeks), then reinfusing them into the person so they can provide an enhanced immune response. Two examples of T-cell therapies are TIL (tumour-infiltrating lymphocyte) therapy and CAR (chimeric antigen receptor) T-cell therapy.

Monoclonal antibodies and checkpoint inhibitors

Monoclonal antibodies are produced by a single clone of a specific type of white blood cell. They act as the key in cell lock-and-key mechanisms and can target specific cell types. Checkpoint inhibitors are a particular type of monoclonal antibody whose role is to block lymphocyte off-switches, ensuring lymphocytes remain active in an immune-mediated elimination of malignant cells. The side-effects of checkpoint inhibitor therapy can be serious as any organ can be adversely affected by an overactive immune response. This includes a risk of neuropsychiatric side-effects, including depression, anxiety, insomnia, fatigue, suicidality and psychosis.

TABLE 3 **Types of RNA therapy**

Therapy	Description	Examples of therapeutic use
Anti-sense oligonucleotides	A short strand of synthetic RNA pairs with messenger RNA (mRNA) in the cell to modulate how 'splicing' of coding and non-coding regions occurs Anti-sense oligonucleotides can also bind to RNA in viruses to prevent replication	Defects in RNA splicing occur in Duchenne muscular dystrophy Treatment of cytomegalovirus
Small interfering RNAs (siRNAs)	These short double-stranded RNA molecules occur naturally in the cell and are responsible for 'RNA interference', whereby they can bind with mRNA and flag it for destruction, hence regulating gene expression. siRNA molecules can be produced synthetically as therapeutics	Treatment of hypercholesterolaemia
Exogenous mRNA	Synthetic mRNA is delivered to the cell, where it is used by the cellular machinery to produce proteins which trigger an immune response	Cancer vaccines, e.g. for metastatic melanoma SARS-CoV-2 vaccines
RNA aptamers	Aptamers are short single-stranded nucleic acid molecules (can be RNA or DNA) that fold into a very specific 3-D shape and can then bind to proteins to modulate their function	Macular degeneration

mRNA, messenger RNA.

Current clinical uses of monoclonal antibodies include:

- treatment of infection, for example to treat mild to moderate COVID-19 where the patient is at high risk if the illness were to become severe
- treatment of chronic inflammatory disease such as arthritis and Crohn's disease
- use as a component of diagnostic indicators, for example to detect pregnancy, ovulation, menopause and myocardial infarction.

Immunotherapy and psychiatry

Although immunotherapy is typically associated with cancer (it is anticipated to become the main type of cancer treatment (Yang 2022)), there are psychiatric conditions where immune responses are likely to be playing a role and therefore where there is the potential for immunotherapy. Immunopsychiatry is an emerging subspecialty that currently has the potential to gain further interest through topical immunopsychiatric hypotheses about why an estimated 34% of people have developed a new neurological or psychiatric condition within 6 months of having COVID-19 (de Picker 2021). There is also increasing interest in the role of inflammation in major mood and psychotic disorders and calls for immunological screening in all cases of new or treatment-resistant mental illness. Alongside this, immunotherapy has potential as future treatment – there is growing evidence that immunotherapies and other anti-inflammatory medications may have a role in managing severe mental illness, especially in the early phases of psychosis (Cakici 2019).

Autoimmune encephalitis is worthy of specific mention because of increasing recognition that this can present atypically as a neuronal antibody-positive psychosis that responds to immunotherapy. In 2020, an international consensus on diagnosis and management was released (Pollack 2020).

What next for immunotherapy and psychiatry?

Finding and having a better understanding of predictive biomarkers for immunotherapy would help us to better understand who will and who won't benefit from such treatments as, although only a minority are likely to respond, those who do tend to respond very well.

Stem cells

Stem cells are primitive, relatively undifferentiated cells capable of dividing and developing into the specialised cell lines that make up the tissues of the human body. Stem cells in the embryo ('embryonic stem cells') are pluripotent, meaning they can develop into any cell type. Stem cells are also found in adults ('adult stem cells'). Adult stem cells are multipotent, not pluripotent – the repertoire of cells they can give rise to is more restricted. For example, it has long been recognised that adult stem cells are found in bone marrow that can differentiate into the various types of mature blood cells, but not other cell types. More recently, adult stem cells have been discovered in a range of tissues, including the brain ('neural stem cells', which are particularly found in the subgranular zone of the dentate gyrus and the subventricular zone). Neural stem cells underpin neurogenesis in the adult brain and are an important potential target for future therapies in neurology and psychiatry.

To the two broad families of naturally occurring stem cells, embryonic and adult, can be added a third, artificially created type – 'induced pluripotent stem cells' (iPS cells). In one of the most important biotechnology papers published so far in the 21st century (Takahashi 2006), Shinya Yamanaka and his colleague Kazutoshi Takahashi demonstrated how the introduction of four genes into adult fibroblasts could induce them to 'regress' back into undifferentiated pluripotent stem cells. Yamanaka was awarded the 2012 Nobel Prize in Physiology or Medicine for this research (shared with the British researcher Sir John Gurdon, who had carried out earlier seminal work on cell nucleus transplantation).

The creation of iPS cells has opened up three key avenues of research (Scudellari 2016):

- stem cell therapies
- use of iPS cells to model disease processes and identify biomarkers – for example, how autism risk genes affect neuronal development and synapse formation
- use of iPS cells to develop and test new drugs.

Despite the obvious attraction of using iPS cells to treat degenerative disorders such as Parkinson's disease or age-related macular degeneration, progress has been limited so far in the direct use of stem cells as therapy. This has been due to several factors, including some poorly conducted initial trials, concerns about possible neoplastic risk and hence the need for complex approval processes.

Within psychiatry, although there are no approved treatments, Zhang et al (2020) have provided a review of areas of research in stem cell therapeutics. These include stimulating the brain's own neural stem cells or introducing iPS cells to restore abnormal myelination and/or connectivity in severe mental disorders such as schizophrenia or bipolar disorder and using stem cells to replace lost populations in degenerative conditions such as Alzheimer's disease.

The impact of iPS cell research so far has been much more substantial in the second and third areas listed above, where the technology has allowed the creation of cell lines and tissues in which disease processes and pharmacological treatments can be modelled (Scudellari 2016). This

research will be aided by the discovery that iPS cells have the capacity for histogenesis and can differentiate to produce the varied cell types that make up an organ, for example 'brain organoids', which mimic in a simplified form the structure of the developing brain (Zagorski 2021). This, however, brings into sharper relief ethical issues, which have always accompanied aspects of stem cell research.

The gut microbiome

A microbiome is the community of micro-organisms (bacteria, viruses, protozoa and fungi) that live in a certain place. In terms of genetic material in our bodies, it has been previously suggested that microbial cells outnumber human cells in a 9:1 ratio, although more recent research suggests the balance may be closer to 1:1.

Gut microbiome development in early life can influence neurodevelopment and later in life can affect mental health, as the gut and brain have two-way communication through hormone, nerve and immunological pathways. Changes in microbiota can result in harmful bacterial changes that can adversely affect brain function. Stress is associated with a change in microbiota composition in a variety of mammals and, in another example of bidirectional interactions, the gut microbiome regulates the stress response (with probiotics being able to protect against the negatives effects of stress). The gut microbiome and its interactions with the brain have been implicated as having a role in mood and anxiety disorders (including bipolar affective disorder), schizophrenia, autism (where there is a strong association between the severity of an autism spectrum condition and the presence and severity of gastrointestinal conditions), attention-deficit hyperactivity disorder and Alzheimer's dementia. New research has found that gastrointestinal and psychiatric conditions have a widespread shared distribution of genetic associations. This supports a genetic element to the gut–brain axis and has significance when considering treatment of conditions affecting the gut and the brain (Gong 2023).

Interventions that target the microbiome (such as dietary changes, pre- and probiotics and faecal transplantation) have the potential to treat mental illnesses. It is also feasible that manipulating the gut microbiome could prevent development of mental illnesses (Leza 2020) and that psychotropic medications (especially antipsychotics and most antidepressants) affect the gut microbiome (Bastiaanssen 2019). There has even been a suggestion that transcranial magnetic stimulation can lead to an increase in anti-inflammatory intestinal bacteria and an associated reduction in weight in obesity (Ferrulli 2018).

What next for psychiatry and the gut microbiome?

Dietary changes for better mental health are likely to become normal interventions in due course. It is also feasible that pre- and probiotic 'psychobiotics' may become treatments alongside current interventions. The challenge is to translate and mobilise knowledge from preclinical research into real-world psychiatry (see also Box 2).

Neuroimaging

The understanding of the structure and functioning of the brain in health and disease has been radically transformed by developments in neuroimaging over the past 30 years. A detailed discussion of this literature is beyond the scope of this paper, but a useful summary of the impact of neuroimaging in psychiatry is provided by Silbersweig (2017).

Advances in magnetic resonance imaging (MRI) have allowed more detailed analysis of whole and regional brain grey matter volumes as well subcortical white matter tract integrity. Technologies such as positron emission tomography (PET), single-photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) have enabled *in vivo* real-time assessment of brain activity across a range of psychiatric disorders and in healthy controls. This has allowed associations to be made between the experience of symptoms (e.g. hallucinations) and certain parts of the brain, particularly when the patient is given activation tasks to perform in the scanner.

Using 'connectivity analysis' to understand correlations between activity levels in different regions of the brain has allowed a more complex appreciation of how circuits and wider network connections are affected in psychiatric disorder, not simply specific

BOX 2 The gut–brain axis: implications for psychiatrists

Having a healthy microbiome is likely to help psychological well-being. There are too few human trials to fully understand the details of this but dietary changes that could help include (Butler 2019):

- using probiotics with certain strains of *Bifidobaceterium* or *Lactobacillus* in them might help manage anxiety and depression
- increasing intake of fermented foods can help ensure a healthy microbiome (but it is unclear how well this translates to direct benefits to mental health)
- prebiotics may also help; they are found in several fruit, vegetables and wheat products
- a Mediterranean diet provides some protection against depression

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localised areas. It is becoming increasingly possible to understand psychiatric disorder in terms of disturbances in core neurocognitive processes such as emotion regulation, salience evaluation and executive function.

Although these findings have yet to have significant direct utility in the clinic, they present important steps on the journey of personalised medicine, allowing a move away from an essentially syndromal definition of psychiatric disorder to more fundamental understanding of disease mechanisms, with clearer delineation of patient subgroups and possible future targets for neuromodulatory therapies.

Neuromodulation/neurostimulation

'Neuromodulation' is the modification of nerve activity using targeted electrical, magnetic or chemical stimulation. Electromagnetic techniques can be broadly referred to as 'neurostimulation', i.e. a subset of neuromodulation. Neurostimulation has a long history in psychiatry, most notably in the form of electroconvulsive therapy (ECT), but there are now a wide range of neurostimulatory therapies used in a variety of contexts across medicine. A simple, non-exhaustive classification of neurostimulatory therapies is shown in Box 3, and we give notes on three of the newer techniques most relevant to psychiatry below.

Deep brain stimulation

In deep brain stimulation (DBS) an electrode is placed in a deep structure within the brain and connected via a wire to a battery implanted subcutaneously on the chest wall. The electrical stimulation profile delivered through the electrode can be changed according to the clinical context. In more advanced systems, the stimulation delivered is modulated by measurement of brain activity in the target area (closed-loop DBS). There are similarities to the use of pacemakers in cardiac medicine. The exact mechanism of action of DBS is not clear but is likely to relate to effects on neurogenesis and synaptic functioning.

DBS is approved by the National Institute for Health and Care Excellence (NICE) as a treatment for Parkinson's disease, dystonia and (under special circumstances) epilepsy (Interventional Procedures Guidance IPG19, IPG188 and IPG678 from www.nice.org.uk/guidance). Research is ongoing to establish efficacy of DBS in psychiatry (Sullivan 2021). Owing to a limited evidence base NICE recommends that DBS is used only in research into obsessive–compulsive disorder (OCD). It has not been specifically evaluated by NICE for other conditions. There is some evidence of efficacy in treatment-resistant depression (Figee 2022) although response rates are wide, particularly in open-label studies. Further research is needed on which brain regions/tracts to target (subcallosal cingulate gyrus is the most common), stimulation protocols and outcome measures. Limited data suggest that DBS may be beneficial in the depressive phase of bipolar disorder (Mutz 2023) but again further research is required.

BOX 3 Neurostimulatory therapies

Invasive neurostimulatory therapies:

- Deep brain stimulation (DBS)
- Vagal nerve stimulation (VNS)
- Spinal cord stimulation
- Peripheral nerve stimulation

Non-invasive neurostimulatory therapies

- Transcranial magnetic stimulation (TMS)
- Electroconvulsive therapy (ECT)
- Magnetic seizure therapy (MST)
- Transcranial direct current stimulation (tDCS)
- Transcranial alternating current stimulation (TACS)
- Transcutaneous auricular vagal nerve stimulation (taVNS)

Repetitive transcranial magnetic stimulation and transcranial direct current stimulation

In repetitive transcranial magnetic stimulation (rTMS) a repetitive electric current is passed through a wire coil placed against the scalp. The magnetic field generated induces current, and thus depolarisation, in the cortex under the coil. Similarly, transcranial direct current stimulation (tDCS) also modifies cortical excitability, but in this instance a low voltage direct current is passed between two electrodes placed on the scalp.

Both treatments remain limited in use at present owing to heterogeneity in the evidence base (Hyde 2022). NICE guidance (IPG542) is that rTMS can be used as a treatment for depression with normal arrangements for clinical governance and audit in place. It has adequate evidence of efficacy with no major safety concerns. It should be used only in research contexts for treatment of auditory hallucinations or OCD, because of inadequate evidence of efficacy. NICE recommends that although tDCS shows some evidence of efficacy in depression there are 'uncertainties about the specific mode of administration, the number of treatments needed and the duration of effect' (NICE 2015: para. 1.1). It notes that tDCS should be used only with special arrangements in place for clinical governance, consent and

audit or research. More detailed reviews of the clinical efficacy and adverse effects of rTMS (Ontario Health 2021) and tDCS (Razza 2020) are available.

Vagal nerve stimulation

Approximately 80% of vagal nerve fibres are afferent, terminating in the nucleus tractus solitarius in the brainstem, which in turn connects to the locus coeruleus. In vagal nerve stimulation (VNS) a pulse generator is implanted which connects to a helical electrode around the left vagal nerve to stimulate these afferent pathways and connected brain regions. Vagal nerve stimulation has been approved by the US Food and Drug Administration for treatment of drug-resistant epilepsy and depression. NICE approves its use in treatment-resistant epilepsy (NICE Guideline NG217), but advises that it should be used in treatment-resistant depression only if special arrangements are in place for clinical governance, consent and audit or research, owing to limitations in quality of evidence for efficacy (IPG679).

Like DBS, vagal nerve stimulation is an invasive procedure that poses risks due to surgery and insertion of a foreign body. Non-invasive forms of VNS are being trialled (Kong 2018), such as stimulating parts of the ear where the skin is innervated by afferent vagal fibres (transcutaneous auricular VNS).

New drug treatments

Psychiatry benefited from the development of a range of pharmacological treatments after the Second World War. Serendipity (backed up by careful clinical observation) played a large part in many of these discoveries, with drugs developed initially for other indications finding a place in psychiatric practice. In turn, the mechanisms of action of these drugs led to hypotheses about the aetiology of the disorders they were treating, centred on abnormalities in monoamine transmission (e.g. the dopamine hypothesis of schizophrenia, serotonergic models of depression). These hypotheses have had variable levels of evidential support but have struggled to provide a robust and comprehensive explanation for pathogenesis.

Disappointingly, even in recent decades most new psychotropic medications have been variations on the pharmacology of existing medications. In the period from 2011 to 2021, only 12 new psychiatric drugs were approved by the US Food and Drug Administration (FDA), compared with 50 in neurology and 135 in oncology. The majority of these psychiatric drugs were 'me-too' compounds similar to existing psychotropics. From 2015 to 2021, the FDA approved 2 'first in class' drugs in psychiatry (brexanolone and lofexidine), 13 in neurology and 31 in oncology (Howes 2023).

Table 4 summarises some of the areas of novel drug development in psychiatry. As can be seen, there is variation in the degree to which these drugs relate to presumed fundamental disease mechanisms, i.e. are 'translational'. For example, psychedelics follow a more traditional route of a drug being found to have an effect experimentally, with backwards investigation into possible mechanisms, whereas 'sestrin modulators' that stimulate synaptogenesis are being trialled based on effects on one of the likely areas of pathogenesis in depression.

Artificial intelligence

The potential for artificial intelligence, i.e. the development of computer systems capable of undertaking tasks that normally require human intelligence, has received much attention in psychiatry as in other branches of medicine (Fakhoury 2019; Pham 2022). The origins of artificial intelligence go back further than we might imagine, and as early as the 1960s a computer program known as ELIZA was developed to emulate the conversational prowess of a psychotherapy (Pham 2022).

Artificial intelligence has since moved to encompass neuroimaging studies to classify and diagnose people with mental health conditions (Pham 2022). Chatbots, i.e. computer programs that can replicate conversations with users via a chat interface (either text- or voice-based), have also generated significant attention (D'Alfonso 2017).

Chatbots can make use of natural-language processing and machine learning. Natural-language processing relates to the ability of computers to understand and manipulate humans' natural language and machine learning is the ability of a computer program to grow and adapt when confronted with new data, even when it has not been explicitly moved to do so (D'Alfonso 2017). Deep learning is a type of machine learning that uses multiple layers to progressively generate higher-level features from the raw data (Ray 2022). For example, in an image recognition application, the raw material could consist of a matrix of pixels and the end-stage via deep learning may be an image of the brain (Ray 2022). Studies involving EEG deep learning have been used to differentiate between people with depression and controls with 90% accuracy (Saeedi 2021), and machine-learning algorithms have successfully differentiated healthy controls from people with psychotic disorder with more than 70% accuracy (Antonucci 2021) and been successfully used in suicide prediction models (Kusuma 2022).

Avatar therapy is also an emerging area, with companion bots such as Paro (a robotic seal) and eBear

TABLE 4 **Novel drug development in psychiatry**

Mechanism of action	Examples	Notes
Glutamate pharmacology	Esketamine – NMDA antagonist Luvadaxistat – an amino acid oxidase inhibitor which increases glutamatergic transmission Iclepertin – inhibitor of presynaptic glycine transporter 1 (GlyT1)	Esketamine is the first FDA-approved drug for depression not based on monoamine pharmacology Under investigation for negative symptoms in schizophrenia Designated as 'breakthrough therapy' for cognitive impairment in schizophrenia by the FDA
Neuroactive steroids – wide-ranging genomic and ion channel effects	Allopregnanolone (brexanolone)	FDA approved for intravenous treatment of postpartum depression. An oral form, zuranolone, is being trialled in treatment-resistant depression
5-HT_{2A} agonism	Psychedelics, especially psilocybin	Under investigation across a range of psychiatric indications (Tullis 2021). Psilocybin (depression) and MDMA (PTSD) approved in 2023 for specialist use in Australia
Orexin pharmacology	Orexin antagonists, e.g. suvorexant	Suvorexant is licensed in some parts of the world as an insomnia treatment and is under investigation as an augmenting agent in depression treatment
Immune regulation	$P2X_7$ antagonists	Under investigation as a treatment for depression
Muscarinic agonists	For example KarXT (combination of xanomeline, a central M_1/M_4 agonist, and trospium, a peripheral muscarinic antagonist)	Under investigation for treatment of positive and negative symptoms of schizophrenia
Stimulators of synaptogenesis	Sestrin modulators such as NV-5138	Under investigation as treatment for depression

NMDA, *N*-methyl-D-aspartate; FDA, US Food and Drug Administration; MDMA, 3,4-methylenedioxymethamphetamine ('ecstasy'); PTSD, post-traumatic stress disorder.

MCQ answers
1 c 2 c 3 d 4 a 5 b

(an expressive, bear-like robot) being developed as a tool to interact with patients with the aim of improving psychiatric outcomes (Pham 2022), for example in schizophrenia (Ray 2022) and for children with autism spectrum disorder (Ray 2022).

Brain–computer interfaces (BCIs) are also an emerging area. BCIs acquire brain signals, analyse them and put them into commands which are transmitted to output devices that deliver desired actions (Shih 2012). They do not rely on normal neuromuscular output pathways and their aim is to replace or restore useful functions to people disabled by neuromuscular disorders such as stroke, cerebral palsy or spinal cord injury. BCIs can operate many different devices, such as cursors on computer screens, robotic arms and wheelchairs (Shih 2012). In the future, it is hoped that it will be possible to convert external signals into human neural activity, such as sight restoration (www.neuralink.com).

The artificial intelligence neural network model AlphaFold shows huge promise in determining the three-dimensional structure of proteins on the basis of amino acid sequence, a previously highly labour intensive and complex task for scientists (Jumper 2021).

The use of artificial intelligence innovations arguably has great potential, particularly in the context of the significant burden of mental illness in society and the labour shortage in the mental health workforce. It has also been argued that chatbots and avatar therapy may even have some intrinsic advantages over their human counterparts as it may reduce a patient's experience of stigma if they are able to confide in a less 'personal' machine than the potential shame involved in talking to a real person (Pham 2022). It is, however, clear that bots and avatars cannot possess the full range of emotional awareness and empathetic responses a highly trained and skilled human could offer (Pham 2022).

Conclusions

The technologies described in this article offer wide-ranging potential to improve the understanding, diagnosis, treatment and possibly prevention of mental disorders. There is the opportunity for increased personalisation of care and, if used wisely, deeper integration of the biopsychosocial approach in psychiatry. However, there are risks too, from an unthinking biological reductionism in which the complex lived experience of the patient is lost, through to complex ethical concerns particularly in fields that fundamentally challenge what it means to be human. It is important that psychiatrists have an overview of these technologies as they continue to shape the world around us.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

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Declaration of interest

None.

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Multiple choice questions

Select the single best option for each question stem

1 Which of the following is **not** a potential benefit of translational approaches in medicine?
- a Improved strategies for disease prevention
- b Identification of novel therapeutic targets
- c Strengthening of the approach of using descriptive disease categories
- d Individualised prediction of disease risk
- e Personalised treatment planning.

2 Which psychotropic may, in part, act through modulating the acetylation status of histone proteins?
- a Sertraline
- b Clozapine
- c Valproic acid
- d Lithium
- e Diazepam.

3 Immunotherapy is looking especially promising as a potential future treatment in:
- a PTSD
- b new depressive episodes
- c phobias
- d first-episode psychosis
- e early-onset dementia.

4 Between 2015 and 2021, how many 'first in class' psychiatric medications were approved by the US Food and Drug Administration?
- a 2
- b 4
- c 8
- d 14
- e 20.

5 Which of the following is an 'invasive' neurostimulatory treatment?
- a Transcranial magnetic stimulation (TMS)
- b Vagal nerve stimulation (VNS)
- c Electroconvulsive therapy (ECT)
- d Magnetic seizure therapy (MST)
- e Transcranial direct current stimulation (tDCS).