ity[8], and, when supported at one major academic hospital, only 1% of people chose to link their app to their electronic health record[9]. Related, clinicians need training and support to incorporate such new digital health tools. A new workforce will be necessary, with a focus on peer support workers who may mirror the populations that are most impacted by a lack of access to and/or comfortability using technology, and who are ready to provide digital skill training and support.

Achieving optimal health, including mental health, means that we must address social/political determinants of health. Technology literacy now is considered a social determinant of health. It also impacts important aspects of people's lives, such as access to competitive employment, education, and even supportive services such as housing or access to other people, as clearly emerging during the COVID-19 pandemic. All of these aspects directly impact mental health and are as critically important as any clinical-focused use. Acknowledgment and integration of these social determinants can make digital tools more relevant and useful to a broader swath of the population with the highest need.

Thus, supporting digital self-determination should be the first priority, as it will create demand for new privacy protections, inform how the next generation of evidence will generate the highest quality of representative research, and ensure that new health care services are created to serve people with the highest needs. Developing a new generation of digital mental health tools/services to support more accessible, effective and equitable care is the true innovation ready to be stoked today by each person who becomes empowered to connect, set up, engage, start/stop, and demand more from mental health technology.

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The drug treatment deadlock in psychiatry and the route forward

The US Food and Drug Administration (FDA) approved 12 new drugs in psychiatry during the decade 2011-2021 (www.fda.gov/drugs/drug-approvals-and-databases). In comparison, it approved 50 new drugs in neurology and 135 in oncology over the same period. The FDA designated two new drugs as first-in-class in psychiatry (lofexidine and brexanolone) in the most recent reviewed period (2015-2021), compared to 13 in neurology and 31 in oncology (www.fda.gov/drugs/development-approval-process-drugs). These data highlight a dearth of new drug treatments and novel mechanistic approaches across psychiatry, both in absolute and comparative terms. They indicate that psychiatry faces a deadlock in drug development.

One reason for this deadlock is represented by the challenges of conducting clinical trials in psychiatry, due to factors such as high placebo response rates in some disorders, as reviewed by Correll et al[1] in this issue of the journal. These challenges mean that trials have to be large and, consequently, expensive. Large trials generally require many sites, but having more sites has been associated with higher placebo response[1], meaning that this solution may make the problem worse. Another factor is that a number of drug companies – including Pfizer, Eli Lilly, GlaxoSmithKline and Astra-Zeneca – have largely stopped psychiatric drug development. It should be no surprise then that there are fewer new compounds coming through to approval in psychiatry. Finally, it is striking that many of the psychiatric drugs currently in development target the same mechanisms as already approved treatments, with few new classes of medications in the pipeline.

In this situation, the first necessary step is to address some of the challenges in conducting clinical trials in psychiatry. Instead of adding more sites, a potential solution is to use fewer, higher quality sites to minimize noise and reduce the placebo response rate. Another is the use of digital technologies to provide both better standardization of measures and more data. Smart designs also offer the potential to make trials more efficient and informative.

However, addressing these challenges will be of little use if there are no new drugs to test. Companies need to be attracted into psychiatry if we are to see the development of new treatments. There is some light on the horizon: new companies are entering psychiatry in some areas, notably in the development of serotonin 2A receptor agonists, such as psilocybin for major depression and related disorders. Investment in this area exceeded US$500 million in 2021[2]. This is encouraging, but needs to be replicated in other areas of psychiatry if we are to see wholesale progress.

The investment in serotonin 2A receptor agonists is also striking in that it came after well over a decade of research into the use of these compounds by academic groups[3]. This highlights the synergism between academic research and drug development: drug developers grow their ideas from mechanistic and clinical understanding of disorder. It also illustrates the need for sustained investment in translational research in psychiatry to sow the seeds for future drug development. This requires the engagement of governments and charitable funders. It is noteworthy, in this respect, that both neurology and oncology have seen large-scale, long-term research investment from charities such as Can-

cer Research UK and the Michael J. Fox Foundation, which psychiatry has not seen.

Another potential strategy is to form pre-competitive partnerships between companies and academia to generate the clinical evidence in an area to guide future drug development. Governments and regulators could also incentivize companies to invest in psychiatric drug development through, for example, tax breaks or longer patent recognition, in consideration of the challenges and unmet need in psychiatry.

Much psychiatric drug development has been based on astute clinical observation and empirical studies, followed by extensive efforts to then develop related compounds. This has given us a wide choice of medications for some conditions but few mechanistically distinct treatments. We have harvested serendipity's bounty over many decades now and, it seems, there are few low-hanging fruits left.

It is striking how much remains to be established about the link between pathophysiology and psychiatric symptoms[e.g.,4]. To develop mechanistically new treatment approaches, we will need to advance understanding of the neurobiology underlying psychiatric disorders; in particular, of the link between molecular processes and symptoms, to be able to identify new molecular targets for drugs. We also need to recognize that psychiatric disorders usually involve multiple brain systems and show clinical heterogeneity. Accordingly, successful treatment approaches of the future may need to be promiscuous in their targets and/or we will need to address clinical heterogeneity, for example by subtyping disorders to particular systems that can be targeted by more selective drugs[5,6]. This will require investment in research into neurobiology, for example in post-mortem or molecular imaging studies, and the link to psychological processes and social factors.

We also need to understand the neurobiology underlying poor response to existing treatments, not least because this is where some of the greatest unmet needs lie[7]. This has not been a focus for research traditionally, but evidence is beginning to accrue that there are neurobiological differences linked to poor treatment response, for example in schizophrenia[6,8], that identify new treatment targets[7].

Greater understanding of the neurobiology underlying psychiatric symptom domains will support the development of biomarkers that can be used to identify the right patients in whom to test a given drug, and to evaluate the effects of that drug. Furthermore, we need preclinical models that reproduce the neurobiology seen in patients. Back translation from patient findings, as has been done for the elevated striatal dopamine synthesis capacity seen in schizophrenia[9], is one approach. Another is the use of stem cell technologies that allow drugs to be tested in neurons derived from patients.

Overall, whilst in the short term strategies can be implemented to improve the design of clinical trials, ultimately much more research into the neurobiology of psychiatric disorders will be needed if we are to see the step-change in treatment approaches that has been observed in neurology and oncology.

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