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## The World Psychiatric Association (WPA)

The WPA is an association of national psychiatric societies aimed to increase knowledge and skills necessary for work in the field of mental health and the care for the mentally ill. Its member societies are presently 145, spanning 121 different countries and representing more than 250,000 psychiatrists.

The WPA organizes the World Congress of Psychiatry every year. It also organizes international and regional congresses and meetings, and thematic conferences. It has 66 scientific sections, aimed to disseminate information and promote collaborative work in specific domains of psychiatry. It has produced several educational programmes and series of books. It has developed ethical guidelines for psychiatric practice, including the Madrid Declaration (1996).

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1. Cuijpers P, Sijbrandij M, Koole SL et al. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry* 2014;13: 56-67.
2. McRae TW. The impact of computers on accounting. London: Wiley, 1964.
3. Fraeijls de Veubeke B. Displacement and equilibrium models in the finite element method. In: Zienkiewicz OC, Hollister GS (eds). *Stress analysis*. London: Wiley, 1965:145-97.

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# The need for a new generation of digital mental health tools to support more accessible, effective and equitable care

The potential of digital mental health to increase access to and quality of care has gained traction with the rise of smartphones and accelerated with the spread of telehealth during the COVID-19 pandemic. With at least 80% of the global population now owning a device able to capture digital phenotyping signals, analyze data, and run mental health apps, excitement about the imminent arrival of personalized, preventive and precision psychiatry is understandable.

Yet, by nearly all outcome metrics, digital mental health is not transforming care<sup>1</sup>. Whether measured in global trends of deaths from suicide or rising rates of depression, especially among younger people who are often the first to use digital tools, it is clear that the proclaimed paradigm shift is paused<sup>2</sup>. The very people who require mental health care the most, underserved populations, have not experienced a rise in access or boon in outcomes, and the burden of mental illness in low- and middle-income countries remains as high as ever.

Billions of dollars of resources have been poured into health apps, algorithms and devices with the assumption that later, with a simple step, all people would “cross over” or “trickle across” the digital divide and catch up. However, a variety of digital disparities are now emerging, which are troubling but perhaps also addressable. A focus on supporting digital literacy, improving privacy/evidence for these tools, and creating clinical connections each provides tangible steps for more equitable and impactful digital mental health.

As smartphone penetration has accelerated in all countries around the world, blaming the digital divide on a lack of access to devices has become untenable. This narrative now covers lack of Internet access, especially in rural areas. While this is indeed a barrier still requiring work today<sup>3</sup>, it is one that can and will probably be quickly addressed. But, behind access to the Internet, lies a more challenging first inequity – that concerning digital self-determination.

Just as self-determination theory highlights the need for autonomy, competence and connection for psychological thriving, the same is necessary for any digital mental health tools, be they anything from smartphone apps to virtual reality headsets. While the data remain aloof as the topic has not yet been well explored, digital self-determination and the related sub-component of digital literacy remain underdeveloped in populations with the greatest mental health needs<sup>4</sup>.

People may have a smartphone today, but there has not been a concomitant investment in people themselves to ensure that they can equitably engage and benefit from digital mental health tools. Evidence that older adults may find digital health tools more challenging, or that people from underserved backgrounds may engage less certainly, reflects issues with flawed designs of technology and a lack of community engagement, but may also reflect deeper inequities around educational opportunities that today's digital mental health approaches have not yet addressed<sup>5</sup>.

Digital self-determination also means that people may say “no” to using technology for their mental health, and we should honor their choices and voices. A leading reason why people often say “no” is that today digital mental health tools have privacy practices compounded by limited evidence of efficacy. One of the clearest examples of inequity is the lack of privacy offered by most mental health apps. A report by the Mozilla Foundation in March 2022 highlighted ongoing privacy risks among well-known mental health apps. Around the same time in 2022, the suicide hotline service Crisis Textline agreed to stop sharing users' text messages with an outside company after public outcry.

The finding that less than 15% of people in the US and UK are willing to share anonymized personal health information with a company for the purposes of improving health care provides a tangible target for improvement<sup>6</sup>. The lack of trust engendered in health care technology must be reversed, and this can occur with better practices by app developers, demands for privacy by patients and clinicians, and regulation from governments. Without trust, there is no health or mental health, and it is understandable that people do not want their most private and vulnerable information shared in today's digital mental health ecosystem.

Furthermore, despite bold claims of efficacy on their websites, most studies in the mental health field do not recruit or sample from the patients with the highest unmet health care needs<sup>7</sup>. This clear lack of representativeness may explain why many digital technologies fail to offer impressive results in the real world when deployed outside clinical trial conditions. Digital mental health tools need not be perceived as second-class treatments to be utilized when a clinician is not available, but should strive for excellence that exceeds current standards of care. A more subtle but equally insidious bias rests in magnifying current inequalities when machine learning or artificial intelligence algorithms are trained on non-representative populations. As we think of the next generation of studies that can help reverse inequities, it is critical not to justify lower-quality research with the assumption that a digital intervention is better than nothing. If people have a phone, there are many free and effective interventions that can serve as an active control condition (or a digital placebo) to enable actual assessment of efficacy.

Coming to the third above-mentioned inequity, connections matter. As isolation and loneliness are recognized as public health threats, digital health tools will be most impactful when they help people form strong social connections instead of motivating them to continue focusing inward. The full potential of remote monitoring innovations, such as digital phenotyping and wearable sensors, as well as digital behavioral interventions, can only be realized when these are well integrated into care and treatment plans. That means that apps, devices and programs must transfer data to and from electronic medical records and that health workers and their workflow must be part of the design process.

Yet, less than 25% of apps today even allow such interoperabil-

ity<sup>8</sup>, and, when supported at one major academic hospital, only 1% of people chose to link their app to their electronic health record<sup>9</sup>. 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.

John Torous<sup>1</sup>, Keris Myrick<sup>2</sup>, Adrian Aguilera<sup>3</sup>

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1. Torous J, Bucci S, Bell IH et al. *World Psychiatry* 2021;20:318-35.
2. Stein DJ, Shoptaw SJ, Vigo DV et al. *World Psychiatry* 2022;21:393-414.
3. Perrin A. Mobile technology and home broadband 2021. Pew Research Center, June 3, 2021. [www.pewresearch.org](http://www.pewresearch.org).
4. Hoffman L, Wisniewski H, Hays R et al. *J Psychiatr Pract* 2020;26:80.
5. Schueller SM, Hunter JF, Figueroa C et al. *Curr Treat Options Psychiatry* 2019;6: 243-55.
6. Ghafur S, Van Dael J, Leis M et al. *Lancet Digit Health* 2020;2:e444-6.
7. Safavi K, Mathews SC, Bates DW et al. *Health Aff* 2019;38:115-23.
8. Barker W, Johnson C. *J Am Med Inform Assoc* 2021;28:2379-84.
9. Gordon WJ, Patel V, Thornhill W et al. *JAMA Netw Open* 2020;3:e2022408.

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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](http://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](http://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<sup>1</sup> 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<sup>1</sup>, meaning that this solution may make the problem worse. Another factor is that a number of drug companies – including Pfizer, Eli Lilly, Glaxo-SmithKline 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<sup>2</sup>. 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<sup>3</sup>. 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-