Sir William Osler, the great Canadian physician who is considered one of the fathers of clinical medicine, once remarked that the desire to take medicine is perhaps the greatest feature which distinguishes man from animals. 

Maybe patients were different in his day, but, clearly, this is not my experience. Working in an urban community mental health center, one of my biggest challenges is to help patients with a serious mental illness (SMI) like schizophrenia or psychotic bipolar disorder stick with their antipsychotic maintenance treatment to avoid hospitalizations.

Managing adherence is a critical clinical task for chronic disorders like schizophrenia or bipolar disorder as the cost of nonadherence and the resulting pattern of recurring acute illness episodes is potentially high. In addition to reduced medication efficacy over time due to biological changes from frequent relapse, each relapse can have devastating psychosocial consequences, in the form of loss of a job, derailed education, criminal problems, reputational damage, or suicide. Tragically, while antipsychotics are highly effective in preventing psychotic relapse in schizophrenia (number needed to treat [NNT] of 3), adherence is often poor, with almost half of patients taking less than 70% of prescribed doses. Simply prescribing oral medications with no clinical program and strategy to support adherence is therefore not enough for many patients with SMI, particularly when medications need to be taken for many years.

One problem clinicians face is that the assessment of adherence is not straightforward, with no single strategy providing the complete picture. Much clinic time is spent guessing the degree of a patient’s adherence, often missing partial adherence. Self-report is notoriously poor, with patients confidently overestimating their adherence. Clinicians also fall prey to the better-than-average bias that is operative here, judging their own patients’ adherence to be better than comparable patients treated by other clinicians.

Inevitably, technological solutions have emerged to help clinicians assess and monitor antipsychotic adherence more objectively. One early technology was the so-called Medication Event Monitoring System (MEMS) cap in research settings, which could monitor the opening of a pill bottle (but not the swallowing of a pill). The next generation of adherence monitoring tools is represented by more advanced digital medicine systems (DMS) that automatically track the actual taking of a pill. The basic principles of such systems are straightforward: a patient takes a pill that contains a sensor (also referred to as an Ingestible Event Marker [IEM]) that is activated by stomach acid, sending a signal to a wearable sensor patch that in turn sends the information to a mobile device app and, if desired, onto a cloud-based server. Adherence data can be viewed by patients or whomever else has been granted access.

One of the first DMS approved by the FDA in 2017 was aripiprazole with an embedded sensor (brand name Abilify MyCite). Of note, regulatory approval was not based on improved adherence with the DMS compared to usual treatment with an oral antipsychotic, as clinicians may falsely assume. Approval was essentially granted because patients were able to use the system as intended. In this issue of JCP, Cohen and colleagues examine the important question of whether there is true clinical benefit from a DMS for patients with schizophrenia. They conducted a large, industry-sponsored phase 3b trial, using a mirror-image study design in which patients serve as their own control group, before and after the intervention (ie, a switchover from an oral antipsychotic to the aripiprazole with embedded sensor). They found improved adherence that translated into reduced hospitalizations during the 3 to 6 months when patients were using the DMS compared to the period before the switch. This is a good study in that it reports on a real-world and critical clinical outcome (hospitalizations) as opposed to merely a surrogate marker (adherence), although a much longer study is needed to fully assess the efficacy of the DMS. The main limitation of this study is generalizability, however, so I will next discuss how DMS for adherence monitoring may fit more broadly into current and future psychiatric practice.

Importantly, we must not forget that we already have a proven treatment for relapse prevention in the form of long-acting injectable antipsychotics (LAs), which conveniently provide immediate adherence data when patients miss an injection. LAs reduce the relapse risk by 20% to 30% compared to oral antipsychotics. Clinicians should therefore consider the use of LAs as a first-line choice for...
those patients who require maintenance treatment with antipsychotics. Their clinical benefits for relapse prevention are striking for some patient groups like first-episode patients in whom nonadherence rates after an initial hospitalization are very high.\(^9\) Future clinical trials need to compare digital medicine approaches with LAIs, not just with treatment as usual.

For those patients taking oral maintenance antipsychotics, digital medicine adherence monitoring offers an improvement over self-report since nonadherence is detected, the reasons for the lapses can be examined, and tailored, patient-centered solutions can be devised.\(^10\) Like for any treatment or intervention, however, patient selection is key. In a clinical typology of adherence, there are patients who don’t need any help with adherence, those who categorically reject help (and who would “never swallow a spy”\(^11\)), and those who are basically quite willing to take antipsychotics but need help (lack of day structure, cognitive difficulties).\(^12\) As opposed to being misused as a tool of surveillance (a common charge), digital monitoring may increase autonomy in a community-treated patient who needs some medication supervision. Better adherence data fed back to a patient can educate some patients about their suboptimal adherence (challenging the better-than-average bias) and create tailored remedies. Digital medicine may be seen as a tool to engage patients in their own illness self-management in order to reduce the risk of relapse. Other patients may not agree to a LAI because they do not want to get an injection but may be willing to submit to monitoring via digital medicine, including if treatment is court-ordered.

The digital divide is real, and care must be taken that those patients who may have the most to benefit from this technology are not left out.\(^13\) Will the average patient who may have to gain the most from digital monitoring have access to this tool? If anything, introducing a new tool into clinical workflows may cost rather than save money, even if the tool is digital. Is there funding in a clinic budget to pay for skilled support to help the average patient use the technology?

Improving adherence to antipsychotics requires a multipronged approach that ideally combines patient-centered solutions (shared decision making and family engagement), environment-centered solutions (support and supervision), and treatment-centered solutions (choice of antipsychotic and type of delivery).\(^14\) The introduction of a digital medicine tool can improve shared decision making and provide support for those patients who accept treatment but need help with managing their oral medications.

However, moving to the digital world should never replace the most powerful tool we have: a helping human hand. Whatever role digital medicine assumes in a treatment plan, it cannot replace the arduous clinical work of the man in the arena, the clinician working with the patient directly. You should always ask yourself: why not just use a simple pillbox that a family member or visiting nurse helps to fill? I am writing this as an older psychiatrist who is not opposed to technological solutions (although I would not consider myself an early adopter) but who worries about technology replacing instead of augmenting human interactions. For patients with SMI, there are many intangible benefits from real-world interactions with clinicians that are needed for the best possible recovery.

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