

This Section of *Epidemiology and Psychiatric Sciences* appears in each issue of the Journal to stress the role of the epidemiological approach to promote advances in the field of clinical psychopharmacology, with a particular attention to controversial findings. The ultimate aims are to help develop a more critical attitude towards the results of research studies published in the international literature, to promote original research projects with higher methodological standards, and to implement the most relevant results of research in every-day clinical practice. These contributions are written in house by the journal's editorial team or commissioned by the Section Editor (no more than 1000 words, short unstructured abstract, 4 key-words, one Table or Figure and up to ten references).

Corrado Barbui, *Section Editor*

Can a digital medicine system improve adherence to antipsychotic treatment?

D. Papola*, C. Gastaldon and G. Ostuzzi

Department of Neuroscience, Biomedicine and Movement Sciences, Section of Psychiatry, University of Verona, Verona, Italy

A substantial proportion of people with mental health conditions do not adhere to prescribed pharmacological treatments. Poor adherence is probably one of the most critical elements contributing to relapse in people with schizophrenia and other severe mental disorders. In order to tackle this global issue, in November 2017 the Food and Drug Administration approved a tablet formulation of the atypical antipsychotic aripiprazole embedded with a novel digital adherence-assessment device. In this commentary, we critically appraised the potential beneficial and harmful consequences of this new digital formulation of aripiprazole, and we highlighted expected implications for clinical practice.

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Improving adherence to prescribed medicines is key in healthcare, as recently emphasised by the World Health Organization (WHO, 2003). Among people with severe mental disorders, those suffering from schizophrenia and bipolar disorder have particularly high levels of non-adherence, which contributes to the high burden of disability. Indeed, it has been estimated that only one out of three patients with schizophrenia is fully adherent to antipsychotic treatment and that at least 50% of patients are not fully adherent with their medications at some time during the treatment (Marder, 2003). It is worth noting that, among other factors, medication non-adherence is a relevant predictor of relapse (Chen *et al.* 2005).

Among the strategies that community psychiatric services can implement to reduce medication non-adherence in patients with severe mental disorders there are pill counts, electronic devices that capture pill container openings such as the Medication Event Monitoring System (MEMS), bottle caps, pharmacy refill records, mobile phone text reminders, psychosocial interventions such as 'adherence therapy', and even financial reinforces (Nieuwlaat *et al.* 2014). Additionally, long-acting injectable antipsychotics (LAIs) are another frequently used approach to address non-adherence. However, LAIs have been largely criticised for their limited flexibility in dosage control, the pain on the injection site and the culturally rooted idea of them as stigmatising and coercive drugs (Kirschner *et al.* 2013). By contrast, LAIs may notably simplify the daily routine of the patient, reduce the need of control by family members, and can ultimately ameliorate subjective attitude towards medications, and overall quality of life (Das *et al.* 2014).

* Address for correspondence: Dr Davide Papola, Section of Psychiatry, University of Verona, Ospedale Policlinico GB Rossi, Piazzale L.A. Scuro, 10 – 37134 Verona, Italy. (E-mail: candido09@hotmail.it)

A novel medication adherence-assessment device, called digital medicine system (DMS), has recently been designed to assist health-care providers in objectively assessing patient adherence to prescribed medicines. The DMS electronically confirms adherence to oral medication, acquires physiologic metrics periodically and remotely, and presents this information in a centralised manner. Although the DSM technology has been mostly tested in individuals with physical diseases (Frias *et al.* 2017), the first digital medicine released on the market is an antipsychotic. On November 13, 2017 the Food and Drug Administration (FDA) approved 'Abilify MyCite' as the first drug with a digital ingestion tracking system.

Abilify MyCite is a tablet formulation of the atypical antipsychotic aripiprazole embedded with a small edible sensor (1 mm × 1 mm). After the ingestion of the digital medicine, acid fluids of the stomach activate a signal, which is detected by a wearable sensor placed on the chest. The sensor forwards data to an application on the patient's smartphone, which sends data to a cloud-based server. Caregivers and physicians can this way access, through a web-based portal, information on medicine use. Abilify MyCite is indicated in the treatment of schizophrenia, in the acute treatment of manic and mixed episodes associated with bipolar I disorder, and as an add-on treatment for depression in adults. As soon as Abilify MyCite was submitted to the FDA approval process in September 2015, the CEO of Otsuka Pharmaceutical industry called for a 'revolution of the way adherence is measured' (Carson, 2015). The aim of this commentary is to critically discuss how Abilify MyCite may improve treatment adherence, including its potential advantages and shortcomings.

To date, a handful of studies were conducted to shed light on the feasibility of utilising a DMS to electronically confirm ingestion of oral medications using networked sensors in people suffering from severe mental disorders. The first is an observational pilot investigation that enrolled 28 patients with schizophrenia or bipolar disorder and demonstrated that the networked DMS yielded high detection accuracy when compared with directly observed ingestion, and was well tolerated and accepted by patients (Kane *et al.* 2013). Another study, including 67 patients with schizophrenia, yielded similar results, demonstrating also the ability of the majority of patients to use the digital medicine device with good satisfaction, independently or with minimal assistance (Peters-Strickland *et al.* 2016). An 8-week, single-arm trial that enrolled 49 patients diagnosed with schizophrenia, bipolar or depressive disorder suggested that an integrated call centre can optimise the use of the DMS (Kopelowicz *et al.* 2017).

A challenging aspect of these studies may be selection bias, as the population enrolled was composed

by individuals who were motivated to participate in the study and to use such a device. Consequently, participants may have been more likely to adhere to the treatment received and possibly more willing to tolerate minor adverse effects (such as erythema or contact dermatitis related to the wearable sensor implant). Furthermore, although participants had a diagnosis of schizophrenia, they had a relatively low level of impairment. Thus, these preliminary studies may have overemphasised the beneficial effects of Abilify MyCite, including its practicality of use in people with severe mental disorders.

Additional important aspects are costs, patient values and preferences. To date, information on the cost of Abilify MyCite on a monthly basis is not available. This hampers the possibility to assess its cost-effectiveness. In term of patient values and preferences, a first consideration is that this device may complicate the patient daily routine, as they should not only remember to take the medication but also deal with all the possible everyday setbacks related to the patch stuck on the chest, such as remembering to change it every week, adherence problems in case of sweating, the possible need to depilate the skin for better adherence. Considering that patients with low illness insight often struggle to comply with relatively simple therapeutic regimes, how can they adhere to such a complex routine? Second, among reasons for refusing medications, perceived coercion and control is often reported and one may argue that this device may likely worsen these subjective feelings, particularly in patients with high levels of suspiciousness, paranoid thoughts and, most of all, experiences passivity and external control of thoughts or body functions. Paradoxically, only patients with good insight and adherence, who would probably not need an electronic monitoring, are most likely to comply with all the requirements related to Abilify MyCite. Third, it is not clear whether the function of the sensor in the pill can be somehow manipulated (for example, by melting the tablet in the water or other liquids).

These considerations lead to the conclusion that while the DMS technology demonstrated the technical capacity to detect and monitor tablet ingestion with high accuracy, acceptable latency and good tolerability, it remains unclear whether this effect may translate into improved adherence in real-world settings. Studies comparing Abilify MyCite with LAIs or other strategies aimed at improving treatment adherence should be conducted to shed light on these issues, and to ascertain its impact on patients' drug attitude and quality of life. In the meantime, considering that 'the ability of Abilify MyCite to improve treatment adherence has not been established' (Otsuka Pharmaceutical Co. 2017), and that the technology

may cast a spooky shadow on the privacy rights of people (Belluck, 2017), it seems difficult to recommend it for everyday clinical practice.

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Conflict of interest

None.

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