Drugs do not work if patients do not take them

Fergus E. Brown, RCPsych Foundation Fellow, Chelsea & Westminster Hospital, London, SW10 9NH, UK

Anthony S. David, Director, UCL Institute of Mental Health, Maple House, London, W1T 7NF, UK

Address for correspondence: fergus.brown3@nhs.net

Telephone number for editorial queries: +447546834396

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Over 70 years have passed since the advent of effective pharmaceuticals to treat mental illness. Since then, innumerable compounds have been researched, developed, and licensed. For all the side effects, monitoring burden, and risk of harm, we now have medications that improve the symptoms and prognosis of mental illnesses. The sticking point is that they only do this if they are taken.

Sub-optimal adherence is a problem throughout medicine – from antibiotic prescriptions lasting days to decades-long statin treatments. Chronic conditions tend to come with more adherence problems – including most psychiatric disorders. Non/poor adherence affects over 30% of diabetes and pulmonary disease patients. Schizophrenia goes beyond this, with meta-analysis of 39 studies yielding a rate of 40-60% depending on measurement methods (Kane et al., 2013).

Does not taking prescribed medications lead to poor outcomes? The answer seems obvious, and evidence is strong that non-adherence increases suicide risk, hospitalisation frequency and duration. The interplay between adherence and hospitalisation is complicated by adherence being factored into insight assessment which independently is associated with these outcomes (David, 2020). It is likely that non-adherence to treatment increases clinicians' perceived need to recommend hospitalisation. The strong correlation between suicide and non-adherence in schizophrenia patients (Hawton et al., 2005) suggests adherence to treatment may have wider benefits than symptom reduction, as do data showing a 19% reduction in all-cause mortality in such patients with 7-11 years of cumulative anti-psychotic exposure (Tiihonen et al., 2009). However, such observational data do not exclude the possibility of confounding, such as more adherent patients leading healthier lives.

A significant challenge for clinicians and patients in improving adherence is a lack of clarity regarding which interventions are most helpful.

One recent review (El Abdellati et al., 2020) assessed 17 studies on interventions and 26 studies on factors related to anti-psychotic adherence. Younger age, cannabis abuse, poor illness insight and severe positive symptoms were associated with non-adherence; positive attitudes towards medications and family involvement were associated with adherence. Side effects, contrary to expectations, were a weak predictor of non-adherence. Family therapy, technology-based interventions, and strategies combining depot medication with psychoeducation were generally found to work, but heterogeneity and methodological weakness limit further conclusions. One RCT demonstrated daily SMS reminders improved adherence, symptoms and quality of life without any impact on illness insight – suggesting that for some patients, remembering to take the medications is the main barrier to doing so.

The usual gold standard RCT format has specific limitations when evaluating adherence. RCTs tend to include patients who are more adherent at baseline than in real world settings, as some engagement is needed to enrol in the trial, excluding the patients most likely to benefit.

Evaluation is further complicated by there being very few ways of accurately measuring adherence. Patient reports are unreliable – forgetfulness, altered beliefs, and wilful misleading introduce significant bias. Pharmacy refills only prove medications are collected; Observing ingestion is resource intensive in outpatient settings and paternalistic. Blood drug levels are subject to wide individual variation, and cross sectional, only providing information about adherence within days to hours (Kane et al., 2013).

Without objective markers of adherence, how does one distinguish between poor response (treatment resistance) and poor adherence?

The latter, sometimes termed pseudo-resistance, represents a significant problem in mental healthcare. Anti-depressant prescriptions in primary care are often given for 6-8 weeks and changed should no improvement be seen at this stage. Adherence to these medications can be as low as 50% (Semahegn et al., 2020). Perceived non-response leads to switching medications, escalating treatment, or, lacking adequate follow up, further suffering from depression.

Long-acting injectable anti-psychotics (LAIs) – depot injections usually administered monthly - reduce treating teams' uncertainty around adherence. They may also increase adherence of their own accord due to reduced reliance on patient memory to take orals. They are more efficacious than oral medication in schizophrenia (Kishimoto et al., 2021) and confer a significant benefit in hospitalisation and relapse. Even longer acting agents are becoming available, with a 3-monthly preparation of paliperidone now licensed for use. They can also be more effective than oral medications in preventing relapse in patients with bipolar or schizoaffective disorders, especially those with predominantly manic symptom profiles. This prompts consideration of LAIs as first line treatment for this subgroup (Pacchiarotti et al., 2019).

LAI's are not a panacea - drawbacks extend beyond adverse effects. A qualitative paper including interviews with mental health nurses details ethical issues raised in administering LAIs, especially under community treatment orders. Doubts regarding efficacy - founded or otherwise - were common, as were requests for non-invasive alternatives. Fears of damage to the therapeutic relationship were universal (Smith and Herber, 2015). There are however international and professional differences in attitudes – doctors being generally more positive about LAIs (Patel et al., 2009).

Long-acting oral anti-psychotics may yield improvements. The only such established medication is penfluridol, a typical anti-psychotic. The drug requires once weekly dosing, and Cochrane review found it to

be equally as efficacious as depots, with lower drop-out rates (Soares and Silva de Lima, 2006). Development of more long-acting oral agents, particularly atypical anti-psychotics to provide alternative side effect profiles, seems to be an underutilised area of research.

Simply paying patients to take their medication works. The FIAT trial showed direct payments to patients of £15 improved adherence to LAIs as well as subjective quality of life. The improvements faded after financial incentives were withdrawn but at 1 year follow up patients did not trend below baseline adherence (Priebe et al., 2016). These results have been replicated (El Abdellati et al., 2020).

Adherence is complex – we have difficulties measuring it, ascertaining how to improve it, and ethical dilemmas actioning strategies that may do just that. Billions of pounds and thousands of man-hours in R&D and production of drugs are all for nought if they remain in the blister pack or pill bottle. The burden of suffering from treatable mental illness demands this issue is resolved

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