Progress in compliance research and intervention: a commentary

ROBERT ROSENHECK

VA New England Mental Illness, Research,
Education and Clinical Center and Yale
Department of Psychiatry, West Haven, CT, USA

Poor compliance or adherence to antipsychotic medication is widely regarded as one of the most important impediments to effective antipsychotic pharmacotherapy and perhaps the one that is most easily remediable.

In their comprehensive review, Kane et al summarize the evidence that, although there is near universal agreement that non-compliance is a major problem in antipsychotic pharmacotherapy, definitions and methods of measurement are quite variable, with some studies suggesting substantially poorer compliance with antipsychotic therapy than with non-psychiatric drug therapies, while others reporting equivalent or even superior compliance for antipsychotic pharmacotherapy.

Much of the variability in the literature on compliance with antipsychotic pharmacotherapy is due to variability and unreliability in methods for measuring compliance, differences in sources of data, and differences in the context in which data is obtained, i.e. whether in carefully managed clinical trials or real-world practice settings.

Perhaps the most remarkable advance presented in Kane et al's review is the recent development of an "ingestible event marker", i.e. a tiny "chip" that is embedded in a capsule of antipsychotic medication and that gives off an electronic signal when the pill comes into contact with stomach acid, a signal that is relayed through a de-identified signal to a remote device that records the exact time of ingestion. This technology would seem to allow, for the first time, precise and completely reliable documentation of

oral medication compliance behavior that can be used to assess any and all definitions of "compliance" and to compare them to each other. Perhaps even more remarkably, this technology has been well tolerated by psychotic patients, evidently without triggering delusions of influence, as many might have expected since such patients not uncommonly have delusions that various wires, or chips have been inserted in their bodies by malicious agents. The measurement problem in the compliance field may, thus, at last have been solved and we can look forward to an explosion of high quality research in this area. The technology may currently be too costly for use in general clinical practice, but it has nearly unlimited potential as a research tool and offers the perspective to eventually bring psychiatry into the digital age, an important advance. As costs come down, as they invariably do with sophisticated technology, the "ingestible event marker" may become a useful clinical tool.

The review also describes a similarly diverse set of psychosocial interventions that have been developed to improve compliance, many of which have been tested in randomized trials and found to be effective in achieving this goal. While promising, the impact of these interventions on the ultimate outcomes of treatment (reducing symptoms and improving quality of life and the chance for recovery in psychotic illnesses) has not been demonstrated. In fact, none of the literature cited seems to have examined whether improved compliance mediates improvements in symptom severity or quality of life, and this would seem to be an important area for research using sophisticated statistical methods, like structural equation modeling, that can test the plausibility of

hypothesized causal mechanisms. The fact that non-compliance leads to poorer outcomes does not necessarily mean that statistically significant improvements in compliance will improve outcomes. Further research is needed to demonstrate that the potential compliance interventions can have real clinical benefits.

Perhaps the most controversial issue in the study of compliance with antipsychotic pharmacotherapy concerns the effectiveness of long-acting injectable (LAI) antipsychotic medication. There have been six recent relatively large randomized trials that found no benefit of LAI over oral treatment (1-6) and only one that found statistically significant benefits, although the comparator oral treatment, quetiapine, may have been underdosed at a maximum of only 400 mg per day by the study protocol (7). In addition to the meta-analysis cited by Kane et al (8), a second recent meta-analysis also found only small benefits of LAI treatment over placebo and no significant benefit over oral medication, but with significantly *increased* extrapyramidal symptoms (9).

Kane et al balance the lack of evidence of superiority of LAI to oral treatment against two kinds of observational studies. A national study from Finland showed reduced risk of re-hospitalization for patients on LAIs (10), but this observational study could not control for potential selection biases either reflecting severity of illness, reasons for initiating LAIs, or other potentially confounding factors. Kane et al also cite a meta-analysis of mirror-image studies (11) that showed reduced hospitalization risk, but such studies are profoundly flawed by regression to the mean and the lack of equivalent control groups. It is suggested that the observational studies have the

advantage of not selecting stable patients, but at least one of the randomized trials (5) and perhaps others deliberately selected unstable, recently hospitalized, high risk patients and found no benefit for LAIs.

Kane et al acknowledge that “non-randomized, open, naturalistic or mirror-image studies can have their own limitations, such as selection bias, expectation bias, and time effect”, but nevertheless suggest that these flaws may be counterbalanced by the fact that they “may more accurately represent the patient population that is most likely to be prescribed LAIs in clinical practice, i.e., patients with adherence issues”. However, the use of inopportune study samples in randomized trials of LAIs has not been demonstrated in any study, and is somewhat countered by two studies related to a LAI trial that did evaluate the representativeness of that sample (12,13). Furthermore, the potential for greater representativeness of a sample cannot undo design flaws that preclude demonstration of causal inferences in pre-post studies and that threaten the validity of Tiihonen et al’s single impressive but inconclusive national observational study (10).

Many clinicians ardently believe that LAI treatment is superior for non-compliant patients, because it gives them certainty that patients who have received injections are getting exposed to medication, at least in the short run. Perhaps this conviction, based on common sense reaction to increased control over patient medication exposure, explains why there is a widespread readiness to dismiss the results of published clinical trials. But if causal relationships between treatments and outcomes are what we need to know about the medications we use, clinical trials remain the definitive tool for evaluating such relationships. As it happens, the evidence from such trials does not support superiority of LAI over oral treatment, even in selected subgroups of unstable, non-compliant patients (14).

It should also be noted that, while observational studies are limited in

determining causal relationships, they are excellent at identifying patterns of real-world service use. Several studies suggest that patients do not stay on LAI treatment for very long, and thus, even if these agents offer benefits while they are used, they may not provide long-term benefits. One study of unstable patients found that only 51% stayed on LAI risperidone for six months (15). A study of thousands of California Medicaid patients found less than 10% completed 6 months of LAI treatment (16). Two large studies of stable LAI risperidone patients found only 51% (17) and 65% (18) completed one year of treatment. According to the US Veterans Affairs administrative data, only 45% of patients stayed on LAI risperidone for 18 months (19). Thus, even if LAI treatment does guarantee access to medicines in the weeks following injection, patients who terminate this treatment derive only short-term benefit. One could argue that even short-term compliance is a meaningful benefit, even if not supported by outcomes in clinical trials, but costs of second generation LAI medications are high and may not be justified by short-term adherence to LAI therapy and lack of randomized trial evidence of benefit.

Kane et al’s paper provides a succinct and comprehensive review of issues of compliance in antipsychotic pharmacotherapy. It introduces the use of the computerized “injectable event marker” to a large audience and this, it can be hoped, will spur innovative research on medication adherence that has not previously been possible. It portrays many areas in which our knowledge is incomplete, controversial and needs development – none perhaps more puzzling than the lack of evidence, thus far, of the superiority of LAI to oral medications in randomized trials.

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Managing non-adherence and the 3 Cs: collaboration, cash and coercion

ANTHONY S. DAVID

Institute of Psychiatry, King's College London, London, UK

On disagreements with players, the late maverick English football manager Brian Clough said: "I ask him which way he thinks it should be done ... we talk about it for 20 minutes, and then we decide I was right".

The review by Kane et al illustrates eloquently just how much we have learned about adherence and non-adherence to treatment interventions in medicine as a whole as well as psychiatry in particular in the last few decades. In reviewing activity in this field recently myself, I noted that as many as 38 systematic reviews had been published on the topic which had themselves been subject to a systematic review (1). The article also covers many diverse approaches to manage the problem, the results of which are somewhat underwhelming. It is here that I believe we should be focussing our efforts.

There are many relatively commonsense things clinicians can do to improve the uptake of medical treatment arising out of this substantial evidence base, from simplifying prescription regimens and addressing side effects, to the use of reminders and prompts. However, making an

impact on chronic, long-term conditions is not so simple and in psychiatry, uniquely, we sometimes have to contend with what might be called clashes of ideology with our patients: when they say there is nothing wrong with them or nothing that the medication can fix. Indeed, as Kane et al suggest, such illness beliefs and lack of insight are the strongest predictors of non-adherence (see 2).

Being alert to side effects of treatment – especially those effects that patients find most obtrusive – is obviously important. However, I think we over-state how much this is really driving non-adherence in psychotic disorders. Patients and clinicians alike may be biased in their perception and attribution of many negative sensations. A person who is sceptical about the value of a particular drug (or drugs in general) is likely to be acutely sensitive to any potentially adverse effect and stop taking it – but the scepticism is the real cause of the non-adherence. The introduction of second-generation antipsychotic drugs was expected to lead to a step change increase in adherence, given their much lower propensity to produce extrapyramidal side effects. This has not happened. Of course, second-generation drugs have their own profile of side effects, with weight gain being noted particularly by female patients in my clinical experience. However, if this were a major driver of non-adherence,

we might expect an objective time lag (and gender difference) between initiation of second-generation antipsychotics and serious non adherence – an interesting hypothesis? Actually, it seems that the trajectory of non-adherence is an exponential decay function like the half-life of an isotope. Roughly speaking, after every 6 months on medication, there is a 50% reduction in adherence.

So, turning to adherence enhancement in psychosis, there is again no shortage of well-conducted and thorough reviews on the topic. The first randomized controlled trial (RCT) of an intervention containing elements of motivational interviewing, cognitive-behavioural therapy, education and good clinical practice ("compliance therapy") was published in full in 1998 (3). When delivered to heterogeneous psychosis patients from South East London admitted to the Maudsley Hospital, their adherence and insight improved by the time they were discharged. Surprisingly, improvements in global functioning were maintained over the subsequent 12-18 months and readmission rates significantly reduced. An attempted replication in Dublin (4) was unsuccessful, perhaps due to low statistical power and less expertise in delivery of the intervention. Because the immediate effects of the intervention were not recorded, we do not know if the intervention