

Medication adherence across the lifespan: Theory, methods, interventions and six grand challenges

To appear in *Psychology & Health* published by Taylor and Francis

G.J. Molloy^{a,b*} and R.E. O'Carroll^c

^aSchool of Psychology, National University of Ireland Galway, Galway, Ireland;

^bWhitaker Institute for Innovation and Societal Change, National University of Ireland
Galway, Galway, Ireland

^cPsychology, School of Natural Sciences, University of Stirling, Stirling, FK9 4LA, Scotland,
UK

Taking medication as agreed with a health care provider 'i.e. adherence', is a critically important health behaviour throughout life for both the prevention and treatment of illness and the maintenance of health (Osterberg & Blaschke, 2005). From childhood use of antibiotics (Baguley, Lim, Bevan, Pallet, & Faust, 2012), to early adulthood use of oral contraceptives (Molloy, Graham, & McGuinness, 2012) to older adulthood use of cardiovascular risk reduction medications (O'Carroll, Chambers, Dennis, Sudlow, & Johnston, 2014), evidence based treatments such as these can have profound impact on health across the lifespan. Variability in the initiation, execution, and persistence of medication taking behaviour plays a significant role in explaining the difference between the trial based efficacy and 'real-world' effectiveness for many medications (Blaschke, Osterberg, Vrijens, & Urquhart, 2012). Medication adherence has therefore been the focus of systematic investigation for several decades by both behavioural and clinical scientists (DiMatteo, 2004).

Despite the long-standing and voluminous research describing the problem of non-adherence, standardised, reliable and feasible evidence based solutions remain elusive and successes have been sporadic and isolated (Nieuwlaat et al., 2014). This shortcoming of behavioural science for medication taking behaviour is not completely at odds with other key health behaviours that require daily maintenance such as smoking cessation, physical activity and dietary behaviour, where similar challenges and modest successes have been encountered for those at high health risk (Bull, Dombrowski, McCleary, & Johnston, 2014). While many of the same key limitations identified in this literature pertain to medication adherence such as an absence of agreed theoretical and measurement approaches and limitations in study designs, medication taking has several fundamentally different behavioural characteristics.

First, the behaviour can only usually be initiated following the granting of permission by a healthcare provider in the form of a prescription and some level of ongoing monitoring of the outcomes of this behaviour by the prescriber. Second, enactment of this behaviour is usually not a relatively prolonged social interaction where social influences of those also engaging in the behaviour can be important determinants, as is often the case for most of the other main behavioural contributors to health, e.g. physical activity, dietary behaviour, alcohol consumption, smoking and sexual behaviour (Mokdad, Marks, Stroup, & Gerberding, 2004). Third, the efficacy of many medical treatments, particularly preventative chronic illness medication is not directly experienced following medication taking behaviour in the form of symptom relief or discernible improvements in vitality, therefore the usual conditions for causal learning are often absent, e.g. slow and small cause-effect relations, other behavioural or medical changes coinciding with the initiation of a medication that may be interpreted as confounders (Rottman, Marcum, Thorpe, & Gellad, 2016). Indeed this role of unambiguous experiential feedback from medication actions is an increasingly acknowledged (McSharry, McGowan, Farmer, & French, 2016), but under-researched aspect of medication

taking behaviour (Phillips, Cohen, Burns, Abrams, & Renninger, 2016). These unique characteristics contribute to the challenge of supporting the maintenance of this behaviour to improve health.

In this special issue, we invited papers from colleagues that addressed key theoretical, methodological and intervention issues related to understanding and optimising medication adherence at various stages of the life course. The 7 papers published in this special issue address each of these 3 areas to varying degrees and provide a useful context to reflect on the science and practice of using psychological approaches to understand and improve medication adherence. While these set of empirical contributions to the literature identify a multitude of research and practice issues we would like to highlight what we see as the 6 grand challenges for progressing science and practice in this area.

Six grand challenges

1. Measurement

The papers led by Dima and colleagues (Dima et al., 2017) and Moran and colleagues (Moran et al., 2017) are both concerned with the challenge of measuring inhaler adherence with the requisite feasibility, validity, reliability and sensitivity to allow progress in describing, predicting and intervening on this behaviour. The findings from Dima suggest that we can improve the way that we assess adherence in the context of asthma by refining how we use self-report methodology (Dima et al., 2017). Examining a specific medication taking behaviour, Moran and colleagues (Moran et al., 2017) intriguing findings show a striking lack of convergent validity between a new electronic method of continuously monitoring the frequency and quality of inhaler adherence and a range of established methods of assessing inhaler adherence. This suggests that commonly used measures may capture a

broad range of phenomena that appear to be empirically unrelated but are conceptually connected as indices of inhaler adherence. These attempts to improve the measurement of adherence provide useful insights, but also cast doubt on the meaning of previous findings in the adherence literature where measurement heterogeneity is common (Nieuwlaat et al., 2014). As in all areas of behavioural science, progress may continue to be slow across the adherence literature until measurement of these behaviours can be improved.

2. Multi-morbidity and polypharmacy

Many studies of adherence have focused on single conditions and single treatments, yet as the population ages many older patients have multiple conditions and are taking multiple treatments. Inauen and colleagues (Inauen et al., 2017) highlight that adherence may vary according to treatment type in those with multiple co-morbidities. Therefore, measures that attempt to capture general adherence may obscure both good and poor adherence for particular treatments. As multi-morbidity and polypharmacy (Barnett et al., 2012) is now the norm for many older adults with chronic disease, this presents a formidable challenge for measurement and intervention and indeed the generalisability of evidence based on single condition approaches. As alluded to earlier, multi-morbidity and polypharmacy also presents a challenge for patients to engage in the causal learning processes that may be necessary for successful initiation and maintenance of medication taking behaviour (Rottman et al., 2016).

3. Feasible psychological targets for intervention

A number of papers included in this issue drew on theoretical models or conceptual frameworks in an attempt to identify specific modifiable psychological targets for intervention. The papers led by Banas, Pesseau and Cahir all attempt to identify key determinants of medication taking behaviour in the context of HIV (Banas, Lyimo, Hospers, van der Ven, & de Bruin, 2017), coronary heart disease (Pesseau et al., 2016) and breast

cancer treatment (Cahir, Dombrowski, Kennedy, Sharp, & Bennett, 2017), respectively. These findings vary in the extent to which they specify intervention targets that are malleable to intervention. While some identified potential targets for intervention can be linked to techniques that are known to be feasible for delivery in relatively low intensity interventions, e.g. perceived behavioural control (Banas et al., 2017) and strategies that reduce the cognitive load and effort required for medication taking behaviour (de Bruin et al., 2017), others refer to broader domains where the specificity and feasibility of related interventions is perhaps less clear, e.g. 'Social Identity' from the Theoretical Domains Framework (Presseau et al., 2016). Ongoing work in the health behaviour change literature is currently attempting to link specific behaviour change techniques with specific constructs or mechanisms of action (Michie et al., 2016) and this may help identify feasible psychological targets for intervention to support medication taking behaviour in diverse conditions.

4. A cumulative evidence base

Building on the previously mentioned challenges relating to measurement and theory we are often faced with an adherence literature that is not cumulative (Nieuwlaat et al., 2014). Standardisation of measurement approaches such as those outlined by Cahir and colleagues (Cahir et al., 2017) can contribute to building a cumulative evidence base. It is frequently the case that quantitative synthesis of RCTs is not possible in the adherence literature despite adequate numbers of studies and relatively homogenous clinical samples (Molloy, O'Carroll, Witham, & McMurdo, 2012). While heterogeneity in measurement and theoretical approaches can contribute to this problem there are several other critical reasons that can prevent the emergence of a cumulative evidence base. As Morrissey and colleagues identify, reporting of methodology and results are often limited in ways that prevent replication and a clear synthesis of evidence (Morrissey et al., 2017). This includes poor reporting, coding and analysis of control or treatment as usual conditions (de Bruin et al., 2010; Oberje, Dima,

Pijnappel, Prins, & de Bruin, 2015). With the increasing mandatory use of reporting standards statements (Boutron et al., 2008; Hoffmann et al., 2014; Vandembroucke et al., 2014) it is likely that the quality of evidence reporting will improve. This will provide the opportunity for the necessary quantitative synthesis of evidence on medication adherence interventions and more reliable estimates of the potential effectiveness of medication adherence interventions on important health outcomes.

5. Comparative effectiveness

The argument for devoting valuable healthcare contact time for improving adherence to anti-hypertensives, for example, is potentially weakened if we know that increasing physical activity might be modifiable, in a similar healthcare interaction, to a degree that would bring about a much greater benefit to blood pressure control and related health outcomes (Naci & Ioannidis, 2013). At present we know remarkably little about the comparative effectiveness of adherence interventions due to the absence of head-to-head trials comparing disparate medical or behavioural intervention strategies. Only if the health gain is substantially greater than alternative forms of healthcare intervention or indeed self-care e.g. physical activity and diet, can we justify devoting significant resources to improving medication adherence.

Therefore, even if we had better measurement and cumulative evaluation of specific effective strategies to improve adherence, we will still need to identify the comparative effectiveness of adherence interventions to alternative uses of healthcare time and resources. The paper by Morrissey and colleagues (Morrissey et al., 2017) gives us an imprecise estimate of the effectiveness of behavioural intervention on a key health metric of adulthood, i.e. blood pressure control, that relates to many health conditions caused by cardiovascular disease. Future work should attempt to systematically assess how these behavioural interventions focusing on medication adherence compare with other potentially effective behavioural

interventions using appropriate health economic analytic methods, e.g. increased physical activity to improve blood pressure control and subsequent health outcomes.

6. Lifespan perspectives

While a number of the health conditions that were the focus of study in the included papers in this special issue can be experienced throughout life, e.g. asthma (Dima et al., 2017) and HIV (Banas et al., 2017), the lifespan perspective does not feature strongly in this set of papers. This may not be surprising given that the samples were predominantly adult participants, however there is scope to incorporate more of the theory and evidence from developmental psychology into understanding adherence to treatment (Modi et al., 2012). In the case of asthma, for example, the psychological barriers and facilitators for inhaler adherence are likely to be very different if someone is seven, seventeen or seventy (Rhee, Belyea, Ciurzynski, & Brasch, 2009). While the paediatric and adult distinctions in supporting adherence are striking, the challenges in supporting self-management of health in adolescence and early adulthood are often not fully appreciated in healthcare (Campbell et al., 2016) or in adherence intervention development. This might reflect the strong emphasis on paediatric and adult medicine in many contexts and the relative neglect of the needs the those are in transition to adulthood (Arnett, 2000). Future work, particularly in relation to life-long conditions, should aim to incorporate our growing understanding of challenges of key life transitions. This will facilitate the design of developmentally appropriate medication adherence interventions.

Conclusion

While these challenges may pertain to the broader health behaviour change literature they have particular resonance for medication taking behaviour. The 7 papers in this special issue

demonstrate that significant progress has been and is continuing to be made in improving our understanding of medication taking behaviour. However, the ultimate goal of developing a range of standardised, reliable and feasible evidence based solutions to poor adherence is likely to remain elusive for many health conditions if these challenges are not overcome.

REFERENCES

- Arnett, J. J. (2000). Emerging adulthood. A theory of development from the late teens through the twenties. *Am Psychol*, 55(5), 469-480.
- Baguley, D., Lim, E., Bevan, A., Pallet, A., & Faust, S. N. (2012). Prescribing for children - taste and palatability affect adherence to antibiotics: a review. *Arch Dis Child*, 97(3), 293-297. doi: 10.1136/archdischild-2011-300909
- Banas, K., Lyimo, R. A., Hospers, H. J., van der Ven, A., & de Bruin, M. (2017). Predicting adherence to combination antiretroviral therapy for HIV in Tanzania: A test of an extended theory of planned behaviour model. *Psychol Health*, 1-17. doi: 10.1080/08870446.2017.1283037
- Barnett, K., Mercer, S. W., Norbury, M., Watt, G., Wyke, S., & Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*, 380(9836), 37-43. doi: 10.1016/S0140-6736(12)60240-2
- Blaschke, T. F., Osterberg, L., Vrijens, B., & Urquhart, J. (2012). Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol*, 52, 275-301. doi: 10.1146/annurev-pharmtox-011711-113247
- Boutron, I., Moher, D., Altman, D. G., Schulz, K. F., Ravaud, P., & Group, Consort. (2008). Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med*, 148(4), 295-309.
- Bull, E. R., Dombrowski, S. U., McCleary, N., & Johnston, M. (2014). Are interventions for low-income groups effective in changing healthy eating, physical activity and smoking behaviours? A systematic review and meta-analysis. *BMJ Open*, 4(11), e006046. doi: 10.1136/bmjopen-2014-006046
- Cahir, C., Dombrowski, S. U., Kennedy, M. J., Sharp, L., & Bennett, K. (2017). Developing and validating a theoretical measure of modifiable influences on hormonal therapy medication taking behaviour in women with breast cancer. *Psychol Health*, 1-19. doi: 10.1080/08870446.2017.1296151
- Campbell, F., Biggs, K., Aldiss, S. K., O'Neill, P. M., Clowes, M., McDonagh, J., . . . Gibson, F. (2016). Transition of care for adolescents from paediatric services to adult health services. *Cochrane Database Syst Rev*, 4, CD009794. doi: 10.1002/14651858.CD009794.pub2
- de Bruin, M., Oberje, E. J., Viechtbauer, W., Nobel, H. E., Hiligsmann, M., van Nieuwkoop, C., . . . Prins, J. M. (2017). Effectiveness and cost-effectiveness of a nurse-delivered intervention to improve adherence to treatment for HIV: a pragmatic, multicentre, open-label, randomised clinical trial. *Lancet Infect Dis*. doi: 10.1016/S1473-3099(16)30534-5
- de Bruin, M., Viechtbauer, W., Schaalma, H. P., Kok, G., Abraham, C., & Hospers, H. J. (2010). Standard care impact on effects of highly active antiretroviral therapy

- adherence interventions: A meta-analysis of randomized controlled trials. *Arch Intern Med*, 170(3), 240-250. doi: 10.1001/archinternmed.2009.536
- Dima, A. L., van Ganse, E., Laforest, L., Texier, N., de Bruin, M., & The Astro-Lab, Group. (2017). Measuring medication adherence in asthma: Development of a novel self-report tool. *Psychol Health*, 1-20. doi: 10.1080/08870446.2017.1290248
- DiMatteo, M. R. (2004). Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care*, 42(3), 200-209.
- Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., . . . Michie, S. (2014). Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ*, 348, g1687. doi: 10.1136/bmj.g1687
- Inauen, J., Bierbauer, W., Luscher, J., Konig, C., Tobias, R., Ihle, A., . . . Scholz, U. (2017). Assessing adherence to multiple medications and in daily life among patients with multimorbidity. *Psychol Health*, 1-16. doi: 10.1080/08870446.2016.1275632
- McSharry, J., McGowan, L., Farmer, A. J., & French, D. P. (2016). Perceptions and experiences of taking oral medications for the treatment of Type 2 diabetes mellitus: a systematic review and meta-synthesis of qualitative studies. *Diabet Med*, 33(10), 1330-1338. doi: 10.1111/dme.13152
- Michie, S., Carey, R. N., Johnston, M., Rothman, A. J., de Bruin, M., Kelly, M. P., & Connell, L. E. (2016). From Theory-Inspired to Theory-Based Interventions: A Protocol for Developing and Testing a Methodology for Linking Behaviour Change Techniques to Theoretical Mechanisms of Action. *Ann Behav Med*. doi: 10.1007/s12160-016-9816-6
- Modi, A. C., Pai, A. L., Hommel, K. A., Hood, K. K., Cortina, S., Hilliard, M. E., . . . Drotar, D. (2012). Pediatric self-management: a framework for research, practice, and policy. *Pediatrics*, 129(2), e473-485. doi: 10.1542/peds.2011-1635
- Mokdad, A. H., Marks, J. S., Stroup, D. F., & Gerberding, J. L. (2004). Actual causes of death in the United States, 2000. *JAMA*, 291(10), 1238-1245. doi: 10.1001/jama.291.10.1238
- Molloy, G. J., Graham, H., & McGuinness, H. (2012). Adherence to the oral contraceptive pill: a cross-sectional survey of modifiable behavioural determinants. *BMC Public Health*, 12, 838. doi: 10.1186/1471-2458-12-838
- Molloy, G. J., O'Carroll, R. E., Witham, M. D., & McMurdo, M. E. (2012). Interventions to enhance adherence to medications in patients with heart failure: a systematic review. *Circ Heart Fail*, 5(1), 126-133. doi: 10.1161/CIRCHEARTFAILURE.111.964569
- Moran, C., Doyle, F., Sulaiman, I., Bennett, K., Greene, G., Molloy, G. J., . . . Mellon, L. (2017). The INCA™ (Inhaler Compliance Assessment™) : A comparison with established measures of adherence. *Psychol Health*, 1-21. doi: 10.1080/08870446.2017.1290243
- Morrissey, E. C., Durand, H., Nieuwlaat, R., Navarro, T., Haynes, R. B., Walsh, J. C., & Molloy, G. J. (2017). Effectiveness and content analysis of interventions to enhance medication adherence and blood pressure control in hypertension: A systematic review and meta-analysis. *Psychol Health*, 1-38. doi: 10.1080/08870446.2016.1273356
- Naci, H., & Ioannidis, J. P. (2013). Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *BMJ*, 347, f5577. doi: 10.1136/bmj.f5577
- Nieuwlaat, R., Wilczynski, N., Navarro, T., Hobson, N., Jeffery, R., Keepanasseril, A., . . . Haynes, R. B. (2014). Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*(11), CD000011. doi: 10.1002/14651858.CD000011.pub4

- O'Carroll, R. E., Chambers, J. A., Dennis, M., Sudlow, C., & Johnston, M. (2014). Improving medication adherence in stroke survivors: mediators and moderators of treatment effects. *Health Psychol*, *33*(10), 1241-1250. doi: 10.1037/hea0000082
- Oberje, E. J., Dima, A. L., Pijnappel, F. J., Prins, J. M., & de Bruin, M. (2015). Assessing treatment-as-usual provided to control groups in adherence trials: Exploring the use of an open-ended questionnaire for identifying behaviour change techniques. *Psychol Health*, *30*(8), 897-910. doi: 10.1080/08870446.2014.1001392
- Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *N Engl J Med*, *353*(5), 487-497. doi: 10.1056/NEJMra050100
- Phillips, L. A., Cohen, J., Burns, E., Abrams, J., & Renninger, S. (2016). Self-management of chronic illness: the role of 'habit' versus reflective factors in exercise and medication adherence. *J Behav Med*, *39*(6), 1076-1091. doi: 10.1007/s10865-016-9732-z
- Presseau, J., Schwalm, J. D., Grimshaw, J. M., Witteman, H. O., Natarajan, M. K., Linklater, S., . . . Ivers, N. M. (2016). Identifying determinants of medication adherence following myocardial infarction using the Theoretical Domains Framework and the Health Action Process Approach. *Psychol Health*, 1-19. doi: 10.1080/08870446.2016.1260724
- Rhee, H., Belyea, M. J., Ciurzynski, S., & Brasch, J. (2009). Barriers to asthma self-management in adolescents: Relationships to psychosocial factors. *Pediatr Pulmonol*, *44*(2), 183-191. doi: 10.1002/ppul.20972
- Rottman, B. M., Marcum, Z. A., Thorpe, C. T., & Gellad, W. F. (2016). Medication Adherence as a Learning Process: Insights from Cognitive Psychology. *Health Psychol Rev*, 1-37. doi: 10.1080/17437199.2016.1240624
- Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gotzsche, P. C., Mulrow, C. D., Pocock, S. J., . . . Initiative, Strobe. (2014). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg*, *12*(12), 1500-1524. doi: 10.1016/j.ijsu.2014.07.014