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Adherence in psychiatry

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The word 'adherence' refers to the provision of consistent support (eg. for a political party or religion) or the act of holding particular elements together (eg. in constructing a building).¹ In the medical context, adherence refers to the extent to which patients take their medications as prescribed.² While the terminology related to medical adherence has changed significantly over the past two millennia, the core issue has not.³ Most recently, the term 'adherence' has replaced the term 'compliance', although it still jostles with 'concordance' in a growing literature which focuses now, as always, on one key question: why do so many people seek treatment for illness but then decide not to take their prescribed medication? This is an important question, both in terms of public health and societal cost: in the US, up to 50% of patients do not take their prescribed medications,⁴ resulting in additional healthcare costs of \$290 billion per year.⁵ The greatest cost of non-adherence, however, relates to prolonged illness, increased rates of relapse and reduced wellness.

Objectives

- After studying this paper, readers should be able to:
- Identify barriers to adherence and predictors of poor adherence
 - Outline the strengths and weaknesses of various methods of assessing adherence

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- Understand and implement strategies for improving adherence in psychiatric practice and verifying progress over time.

Barriers to adherence and predictors of poor adherence

Rates of non-adherence with medication for physical illness are approximately 24% overall, compared with 35% for depression, 42% for psychosis⁶ and 64% for bipolar affective disorder.⁷ Rates of non-adherence are especially high for chronic disorders: in chronic hypertension, rates of non-adherence with medication can exceed 85%, which is comparable to rates of non-adherence with non-medication treatments (eg. diet) which can exceed 86%.⁸ In the mental health context, approximately half of patients who are prescribed antidepressant medication stop taking it after three months.⁹ After a first episode of psychosis, 50% will have stopped taking medication after three months,¹⁰ while over 66% of individuals with schizophrenia are either non-adherent or partially adherent on an ongoing basis.¹¹

Non-adherence is a complex phenomenon or set of phenomena, which are not readily amenable to simplification. Non-adherence can be intentional or unintentional, partial or complete.¹² Even a small deviation from complete adherence can have a significant impact, especially in psychiatry. For example, a patient may report that he or she takes the prescribed medication every day, but may take a selective-serotonin re-uptake inhibitor at night, or a sedating anti-psychotic medication in the morning. These deviations from full adherence, which may relate to both the chronicity of the disorder and the extent of patient insight, may have significant adverse effects that may, in turn, lead to even greater non-adherence in the future.

Non-adherence in psychiatry is associated with a number of

Table 1: Risk factors for non-adherence in psychiatric settings

Patient/disease factors
Depression
Asymptomatic disease
Decreased insight
Cognitive impairment
Positive symptoms in psychotic illness
Alcohol or drug abuse
Medication factors
Complex regimes
Cost of medication
Increased adverse effects

specific risk-factors (see Table 1). Non-adherence is, for example, significantly associated with the presence of psychological problems especially depression.^{13,14} Decreased awareness or understanding of the disease or treatment is also associated with non-adherence; as a result, patients receiving treatment for an asymptomatic disease (eg. maintenance treatment in bipolar affective disorder) have lower rates of adherence.¹⁵ This is also true for patients with decreased insight,¹⁶ those who do not believe in the effectiveness of their treatment,¹⁷ and those with cognitive impairment.^{18,19} The patient-doctor relationship, organisation of follow-up, and patients' non-attendance at outpatient clinics are also risk factors for non-adherence, as is the overall cost of medication.²⁰

While many of these factors are modifiable, some are especially amenable to intervention in an outpatient setting, eg. addressing the complexity of treatment,²¹ side-effects of medication²² and cost of medication.²³ These factors may often be addressed as part of routine care or service re-organisation without an explicit acknowledgement by the treating team or the patient that they are risk-factors for non-adherence. In psychotic illness, it has been shown that high positive symptom scores, current alcohol abuse and recent drug abuse all decrease adherence.²⁴ These too may be amenable to change through the routine revision and re-consideration of therapeutic and management plans in the outpatient setting.

Owing to the diversity of factors likely to underlie the diversity of non-adherence behaviours, however, guidelines from the National Institute of Clinical Excellence recommend that the first step in supporting adherence should be a specific and comprehensive assessment of adherence.²⁵

Methods of assessing adherence

There is no universal gold standard for measuring adherence.^{26,27} Assessment of adherence can take many forms, ranging from simply asking a patient, their family or pharmacist, right up to monitoring blood levels of specific medications. Overall, methods of assessing adherence can be usefully classified into direct and indirect methods (see Table 2).

Direct methods for assessing adherence are thought to provide accurate assessments of adherence, but are generally both costly and time-consuming, and may still be open to

distortion.²⁸ Direct methods include:

Directly observed treatment

This involves staff directly observing patients taking their medication. This method is relatively commonly used with certain patients taking methadone and in inpatient settings. It is also commonly-used outside of psychiatry in the infectious disease setting for treatment of certain cases of tuberculosis. This can be a very helpful method for addressing in non-intentional non-adherence but less so for intentional non-adherence: some people who do not wish to take medication may hide or regurgitate tablets.

Monitoring blood or urine levels of either the drug or its metabolite

This method is commonly used for certain medications such as lithium, sodium valproate, carbamazepine and clozapine. If used appropriately, this approach can provide a helpful, objective assessment of adherence. A number of factors may influence these results, however, including patient factors and drug factors. Patient factors include 'white coat adherence' whereby a patient who is aware of an upcoming blood test may be more adherent in the days or weeks preceding this test, than he or she would otherwise be. Drug levels may be altered by other medications, illicit drugs, certain foods or comorbid disease states. For example, clozapine levels may be decreased by smoking.²⁹ These and other factors may cloud the evaluation of adherence and should be assessed in the history.

In terms of medication factors, a number of important questions need to be asked when evaluating a plasma level. First, was the drug at a steady state when the sample was taken? For a drug to be at a steady state the patient should have been taking the medication for four to five drug half-lives.³⁰ This is of particular relevance with carbamazepine, which takes two weeks to reach steady state³¹ and olanzapine which takes one week. Second, is the timing of the sample correct? Samples should be taken within one to two hours of the recommended sampling time, with trough samples taken immediately before the next dose is due. Third, when was the medication last taken? It is helpful to document clearly the time of the last dose and the time at which the sample is taken. These questions help prevent us from falsely attributing an unexpected plasma level to non-adherence.³²

Overall, plasma monitoring is a helpful and objective assessment of adherence in certain circumstances. However, this method can be influenced by a number of factors related both to the medication and the patient and, consequently, results must be interpreted with care.

Indirect methods of assessing adherence are thought to be less costly, but also potentially less objective, accurate and precise. Indirect methods include:

Self-reporting

This is a central step in the assessment of adherence and has a number of advantages over other methods. It is both simple and inexpensive,³³ and is quick and easy to perform.³⁴ This method has also been shown to be useful in identifying non-adherent patients, as people reporting non-adherence are generally truthful about it.³⁵ One of the big advantages in self-reporting is that, in addition to assessing adherence, it can also elicit personal, social and behavioural factors related to non-adherence,³⁶ ie. in the course of discussing adherence, the patient may identify behavioural factors which reduce adherence (eg. forgetting tablets in the morning when busy getting children ready for school) and may also suggest simple, direct

Table 2: Methods for assessing adherence in psychiatric settings

Direct methods

Directly observed therapy

Blood/urine levels

Indirect methods

Self reporting

Pill counts

Prescription collection

Clinical response

solutions (eg. deciding to take tablets at lunchtime or bed-time instead, when there may be fewer distractions). The understanding gained from this information is often extremely beneficial in maximising adherence and tailoring interventions to the patient's individual circumstances and needs.

Self-reporting is, however, subject to a number of potential limitations, including: over-estimation of adherence due to recall bias; a desire to be seen as working with the doctor; and inaccurate self-observation.^{37,38} It may also be significantly influenced by intra-observer bias.³⁹ Notwithstanding these limitations, a number of factors can improve the accuracy of self-reporting and reduce intra-observer bias. These include: asking about specific time frames; careful wording of questions to ensure a non-judgemental approach; and asking specific questions about adherent practice.^{40,41} Using patient diaries to keep track of their adherence behaviour may also give a truer reflection of behavior⁴², as may the use of validated tools for the assessment of adherence by self-reporting.⁴³

Pill counts

This constitutes another method of indirect assessment of adherence and may involve a range of different methods of documentation of pill usage. Some techniques involve healthcare providers performing unannounced, in-home pill counts and documenting them carefully in situ,⁴⁴ while others involve patients bringing all remaining pills and pill boxes to clinic appointments.⁴⁵ Another variation on this method is the Medication Event Monitoring System, ([MEMS], Apres Corp, Fremont, California) which is a medication bottle cap with a microprocessor that records the time each bottle is opened. This method has been used for a range of medical disorders⁴⁶ and there have been some promising results in relation to schizophrenia.⁴⁷ Most methods of pill counting, however, are open to substantial intentional and unintentional inaccuracy, and are not commonly used in clinical practice as they are not yet thought to provide consistent, reliable information.⁴⁸

Rates of prescription collection

This is another indirect method of assessing adherence, but may lack accuracy in an Irish context as many patients visit a number of different pharmacies, although with patients who regularly use the same pharmacy it may add some helpful information.^{49,50} The information gleaned through this method has the merits of being both objective and relatively easy to obtain, but it may be an unreliable indicator of actual ingestion of medication, especially if medications do not have to be paid for by the patient, and therefore drugs may be dispensed but not taken.

Research in relation to statin cholesterol-lowering medications indicates that the lower the amount the patient needs to pay for medication, the greater their adherence.⁵¹ There is, however, a paucity of information in relation to the effects of a requirement to pay for psychiatric medications, although the use of financial incentives to increase adherence in mental health settings has been examined (see below).

Clinical response

This is not in general a good marker of adherence as it is confounded by too many other factors. But the absence of an adequate clinical response may, in certain cases, provide an indication of the need for a more thorough assessment of adherence.

Strategies for improving adherence

A large variety of methods has been proposed for maximising adherence, ranging from redesigning medication packaging to adherence-focused behavioural therapy. No single approach is likely to work for every patient so it is advised that interventions are tailored to meet the needs of the individual patient.⁵² In general, prophylactic adherence therapy (encouraging those who are adherent to remain adherent) is likely to prove especially valuable. Some of the other most useful and commonly-used methods of optimising adherence include the following (see Table 3):

Choice and design of dosing regime

One of the easiest to implement and least costly interventions is the simplification of the dosing regime, eg. by reducing dosing frequency.⁵³ Patients with non-intentional non-adherence will have the largest benefit and this approach is supported by the majority of the systematic reviews on the topic.^{54,55} In light of these findings, several pharmaceutical companies have developed sustained release preparations of existing medications. Taking this a step further, it is possible that people who wish to adhere to their medications (eg. anti-psychotics) but find themselves unable to manage the dosing regime, may benefit from changing to long-acting, injected depot preparations.

Prescription charges

The use of healthcare is affected by cost. Uptake and adherence are reduced when there is a cost compared to when healthcare is free.⁵⁶ While the cost of buying medications affects adherence in all areas of medicine,^{57,58} it may be a particular problem in relation to mental illness, owing to the especially reduced income levels and broadly-based social disadvantage experienced by the mentally ill.⁵⁹ Lack of insight may also make people less willing to spend money on drugs that they feel they do not need. While this has been addressed, at least in part, by various subsidised and free medication schemes, the cost and availability of medications remain important factors to bear in mind, especially in emergency departments and primary care settings.

Educational and behavioural approaches

Educational and behavioural approaches to optimising adherence have produced mixed results. In schizophrenia, certain types of educational and behavioural approaches have not proven of immediate benefit, although attitudes to treatment at baseline still appear important,⁶⁰ and some promising results have been seen in groups with a strong emphasis on medication adherence, especially those with a behavioural therapy component. One Korean study showed significant improvement in adherence by enrolling the patient in a psycho-educational programme with 'medication

compliance' being a stated component of the programme.⁶¹ The possible role of cultural variables in determining the acceptability and effectiveness of such interventions merits study. There is evidence that attitudes to adherence to psychotropic medication vary significantly between ethnic groups, so interventions may also need to be designed and implemented with an appropriate awareness of ethnic and cultural factors.⁶²

Family psycho-education

Family psycho-education is another approach to adherence that has been studied in some detail. One randomised controlled trial in China compared adherence in patients who received medication combined with family psycho-education with adherence in patients who received medication alone.⁶³ This study showed statistically significant improvement in adherence and reduced relapse in patients who received family psycho-education. The psycho-education approach looked at a number of different areas but specifically addressed medicine adherence.

A similar Italian study showed increased adherence in a group where the family received additional support (weekly support-group meetings focusing on coping skills and stress identification, and the establishment of a social network), as compared with standard information provision. The relative improvement was, however, short-lived and returned to base line after 24 months.⁶⁴ The authors recommended ongoing support for families and commented on the lack of research in this field. There is, in particular, a strong need for studies of (a) the cost-effectiveness of potentially expensive psycho-educational interventions aimed at families, and (b) the potential role of cultural factors in mediating or modulating the effectiveness of such strategies.⁶⁵

Medication packaging

Medication-packaging may not be something generally considered by doctors when writing a script, but evidence shows that medicines packaged in blister-packaging are associated with enhanced adherence,⁶⁶ eg. adherence to malaria treatment is improved significantly through the use of unit-dose packaged medicines compared to medicine in an envelope or bottle.⁶⁷ While most pharmaceutical companies now use blister-packaging, some have gone one step further and printed the days of the week on blister-packs, providing additional support to patients. This may be especially useful for people with impaired short-term memory or difficulties with concentration associated with certain psychiatric disorders.

Multi-compartment medicine systems (MCMS)

MCMS (also referred to as dosette boxes, pill-potting and labelled blister-packs) are containers for medication that divides the medication into different compartments for administration at different times. They not only act as a reminder to take medications but serve as a record of medications already taken. They are used relatively frequently in psychiatry. A recent review of their use in long-term treatments concluded that while good quality research is still lacking, preliminary research results are favourable and, due to the relatively inexpensive nature of the intervention, their use is indicated.⁶⁸ Recent guidelines from the NICE do not recommend across-the-board use of MCMS, but do recommend them in populations that have trouble remembering to take medications and in populations with complex drug regimes.⁶⁹ It is, however, important to note that blister-packing and packing medication into MCMS may be an error-prone process in itself, necessitating supportive education of the patient to empower them to identify their medication within the blister pack, and thus increase the effectiveness and safety of the intervention,

Table 3: Methods for potentially optimising adherence to medication in psychiatric settings

- Revising dosing regimes
- Educational and behavioural approaches
- Family psycho-education
- Medication packaging
- Multi-compartment medicine systems (MCMS)
- Changing formulations
- Reminders (eg. text messages)
- Addressing adverse effects
- Information presentation

an educated, empowered patient is undoubtedly a safer patient.

Formulation

Fixed-dose medications have fewer peaks and troughs in plasma concentrations compared to 'free medicines'. While one systematic review showed fixed-dose formulations improved adherence,⁷⁰ the objectivity of this study has been called in to question.⁷¹ There is, nonetheless, good evidence for improved adherence using fixed-dose formulations as part of dosing regime simplification.⁷² There are currently few examples of this within psychiatry, however, as most formulations have a lack of flexibility in dosing adjustment.

Reminders

The recent guidelines on adherence from the NICE looked at a number of randomised controlled trials and systematic reviews of different kinds of reminders but did not find sufficient evidence to recommend them.⁷³ None of the studies, however, looked at reminders in the context of mental health. The potential role of, for example, mobile telephone text messages ('short message service' or SMS) in mental health settings both merits and requires careful evaluation. There is some evidence that regular text messages can be effective in improving adherence in other areas of medicine, eg. increasing rates of appropriate use of sunscreen,⁷⁴ optimising levels of physical exercise among adolescents,⁷⁵ and increasing adherence with medication for asthma.⁷⁶ Such interventions may, however, be optimally effective in certain groups, such as adolescents, who commonly use mobile telephones; we are not aware of any studies of levels of mobile phone usage amongst individuals with mental illness. In addition, text messaging may raise issues related to confidentiality, as well as boundary issues in the context of psycho-therapeutic relationships, requiring clear agreement regarding the content of, and responses to, text messages.⁷⁷

Financial incentives

There is much debate about the use of financial incentives to promote adherence in healthcare; the issues are at once clinical, ethical and economic. One literature review found that 11 out of 12 randomised controlled trials showed significant improvements in adherence associated with financial incentives.⁷⁸ However, the authors noted limitations on the generalisability of findings as all the studies were carried out in US settings. In addition, all but one of the studies were set outside the field of psychiatry. The sole mental health paper was a 1994 study looking at treatment of cocaine dependence and involving sums of up to \$1,000, but the study was too small to produce significant results.⁷⁹

Financial incentives were not considered in recent guidelines on medication adherence from the National Collaborating Centre for Primary Care, despite the presence of 88 pages on interventions to increase adherence.⁸⁰ Notwithstanding these considerations and unresolved issues, financial incentives are currently being used in the UK, mostly in the field of infectious disease but also in psychiatry. There is, however, a lack of high-quality evidence for this practice, as well as unresolved issues related to ethics, autonomy and dignity.⁸¹

Addressing adverse effects

The most frequently-stated reason for non-adherence is intolerance of side-effects,⁸² and there is evidence that decreasing side-effects improves adherence in both psychosis⁸³ and depression.⁸⁴ Adverse effects may play a larger role in producing non-adherence in psychiatric illness compared to medical conditions. The reasons for this are unclear, but may include decreased willingness to tolerate adverse effects when being treated for psychiatric symptoms as opposed to clearly identifiable physical symptoms (eg. pain), or residual symptoms of mental illness leading to reduced ability to tolerate adverse effects.

Consultation with the patient will provide important information on the severity and importance of adverse effects, and interventions should be tailored to the needs of the individual patient. A formal review of the medication regimen in consultation with the patient, with the explicit aim of minimising adverse effects where possible, may be particularly helpful, especially if this is repeated and reviewed at regular intervals. In certain circumstances, it may be useful to consider the use of newer agents, which may have fewer adverse effects, slow titration of dosing regimens, and utilisation of additional medications to minimize side-effects, if indicated.

Information presentation

As part of other measures to maximise adherence, doctors often provide information about the prescribed medication. Patients are made aware of potential side-effects, duration of these side-effects and other relevant information about the medication and course of treatment. The way that this information is presented has a significant impact on adherence. Two randomised controlled trials have shown that providing patients with written information (or verbal and written information) compared to verbal information alone improves adherence.^{85,86}

Contractual agreement

Current evidence suggests that contractual agreement about medication does not have a significant effect on adherence,⁸⁷ although it remains likely that the quality of the basic underlying patient-doctor relationship does have an effect; further research is needed to clarify this further.

Conclusion

Finally, there is a strong need to follow-up patients in order to verify progress in relation to adherence over time. This can be achieved through the continuation of specific, dedicated methods for assessing and exploring adherence (as outlined above), or by incorporating assessment of adherence as a fully integrated component of routine clinical review at all outpatient clinic visits. The latter approach requires that issues related to adherence are fully integrated into routine clinical practice and become a permanent, recurring element in assessment and management of all patients.

Adherence is an important issue in medicine in general and psychiatry in particular. One of the main problems with research

in this area is the lack of universally agreed methods for measuring adherence, or even definitions of what, precisely, constitutes non-adherence.⁸⁸ Non-adherence is also intrinsically difficult to study because patients who are least adherent with medication are also likely to be least adherent with study protocols.

Notwithstanding these limitations, current literature suggests that the key to maximising adherence is a good assessment of adherence, combined with careful elucidation of reasons behind non-adherence. Potential interventions (see Table 3) should be based on the needs and views of the individual patient, and revised appropriately throughout the course of their illness. In the context of mental illness, it is readily apparent that psychiatric services are strongly relationship-led, and the doctor-patient relationship is likely to play an especially important role in optimising adherence, decreasing symptoms and maximising wellness in this population.

Assessing and optimising adherence may prove initially challenging and time-consuming for busy healthcare providers in day-to-day clinical practice, but non-adherence is such a widespread and costly problem that even small improvements in this field are likely to have far-reaching effects.

Acknowledgement

We are very grateful to the anonymous peer-reviewer for their thoughtful and insightful comments and suggestions.

Declaration of interest: Brendan D Kelly is deputy editor of The Irish Journal of Psychological Medicine but had no role in the editorial process relating to this paper. There is no other interest to declare.

Key online resources

• NICE Clinical Guideline 76: Medicines Adherence – Quick reference sheet for pharmacists⁸⁹, prepared by the Royal Pharmaceutical Society of Great Britain is available at: <http://www.rpsgb.org.uk/pdfs/NICEmedsadhimplementguid.pdf>

• Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence⁹⁰, prepared by the National Collaborating Centre for Primary Care and Royal College of General Practitioners, are available at: <http://www.nice.org.uk/nicemedia/pdf/CG76FullGuideline.pdf> (Nunes V, Neilson J, O'Flynn N, Calvert N, Kuntze S, Smithson H, Benson J, Blair J, Bowser A, Clyne W, Crome P, Haddad P, Hemingway S, Horne R, Johnson S, Kelly S, Packham B, Patel M, Steel J (2009). Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners)

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Multiple Choice Questions

1. Regarding non-adherence:

- Fifty per cent of patients do not take their prescribed medications T F
- Non-adherence is not a problem in mental health settings T F
- In the United States, non-adherence results in additional healthcare costs of \$290 billion per year T F
- Fewer than 33% of individuals with schizophrenia are non-adherent or partially adherent on an ongoing basis T F
- After a first episode of psychosis, 50% of patients will have stopped taking medication after three months T F

2. Regarding drug or urine levels of either the drug or its metabolite:

- A drug will reach steady state after two half lives T F
- A trough level should be taken immediately prior to the administration of a drug T F
- Monitoring of blood or urine levels of a drug or its metabolite is an objective measure which cannot be altered by the patient T F
- Carbamazepine takes two weeks to reach steady state T F
- Correct timing and careful documentation of timing are important in monitoring of levels T F

3. Risk factors for non-adherence include:

- Positive symptoms in psychotic illness T F
- Medications supplied free of charge T F

- Impaired insight T F
- Family involvement T F
- Asymptomatic disease T F

4. Interventions to maximise adherence:

- Should be tailored to the individual patient T F
- Do not significantly improve adherence T F
- Require careful assessment of reasons behind non-adherence T F
- Are easily researched in a high-quality way T F
- Benefit adherent patients T F

5. Regarding methods of improving adherence:

- Multicompartment medicine systems (MCMS) are of no proven use T F
- Contracts with patients have been shown greatly to improve adherence T F
- Psycho-education of the family can improve the patient's adherence T F
- Medication packaging can affect adherence T F
- Financial incentives are being used in certain areas in the United Kingdom T F

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