Title: **Ethical, Philosophical, and Practical Considerations in Adherence to Therapy in Sleep Medicine**

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Introduction

As C. Everett Koop, MD, US Surgeon General, eloquently put in 1985: 'Drugs don't work in patients who don't take them'.

Adherence to treatment may be defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen" [1], while poor adherence to medication decreases treatment efficacy and worsens clinical outcomes [2]. The assessment of treatment adherence is standard clinical practice in a variety of chronic conditions [3,4], however in sleep medicine, measurement of adherence to medicines is limited, rather the only routine adherence measured and addressed is that to positive airway pressure therapy in patients with obstructive sleep apnoea [5].

The phenomenon of non-adherence to therapy, throws up a huge variety of philosophical considerations, including ethical and more practical ones. For the purposes of this review, in light of our disciplinary backgrounds (a respiratory and sleep pharmacist, and a philosopher with interests in addiction), we shall concentrate on issues raised by non-adherence to drug therapies in sleep conditions in particular.

Non-adherence to therapy creates a series of linked philosophical issues. First, the difficulty of measuring rates of adherence creates an epistemic problem regarding the efficacy of prescribed treatments. Secondly, since diseases are often classified as refractory based on apparent failure of standard medicines, the validity of this classification faces a similar epistemic crisis. This in turn produces ethical issues when therapies are restricted to cases deemed refractory. It also calls into question, if the patient doesn't take the medicines as prescribed, what they do with them; and the prospect of potential drug diversion arises. Education of patients seems to be of limited help in addressing these issues; what may be needed is a revision of the patient-prescriber relationship to move away from blame when non-

adherence occurs. We close by revisiting an ancient debate in the philosophy of action which may shed light on what such a revised relationship would require.

Epistemic Issues in Adherence to Therapy

We know that, for a variety of reasons explored elsewhere in this volume, many patients do not adhere to prescribed therapy; but it is difficult to say with any confidence how prevalent this phenomenon is. The WHO reported that adherence among patients with chronic diseases averages only 50% in developed countries [6,7] and recognises this as a significant public health concern due to the impact this has on the health of the individual and significant waste of resources [8,9].

Whatever the reason for their non-adherence [10], patients are understandably reluctant to reveal it to their doctors. Some, already perhaps sensitive about the perception that theirs is not a "serious" condition but an object of fun or whimsy to others, will not want their doctor to think they are not taking the problem seriously. Others may be concerned about the side effects of medicines, lack confidence in their utility or are reluctant to create an impression that they cannot "follow instructions properly", lest they be dismissed as simply lacking discipline and poor sleep hygiene. Still more patients are "eager to please" their doctors, and reluctant to admit that they find a treatment useless, or encounter side-effects they are unwilling or unable to endure for the sake of ameliorating their condition.

Various methods can be used to estimate adherence, though none is much more satisfactory [11]. Inaccurate estimation of adherence leads to unnecessary healthcare spending when the current treatments are deemed ineffective, therefore adding unnecessary therapies or intensifying the original therapies leading to side effects [4,12]. Simply counting the quantity of medicine issued on prescription and comparing it to the intended dose (termed "medicines possession ratio", MPR) will highlight discrepancies that could suggest non-adherence; a patient prescribed one tablet twice a day, for instance, would be expected to be issued with a prescription for around sixty tablets every month by their primary physician. But this may still underestimate non-adherence, as it does not tell us that the patient had the medicine

dispensed from the pharmacy, or that upon receiving it they have taken it as directed [12]. Interrogations of pharmacy dispensing records are logistically more challenging, but nor do they give any more certainty as to whether the patient was adherent to the regimen. Moreover, none of these "work-around" alternatives to patient-doctor disclosure can tell us *why* a course of treatment is not being adhered to.

For all these reasons, and others, doctors have difficulty in establishing whether, and how regularly, patients are taking their medication. And this lack of knowledge, or of reliability at any rate, creates serious epistemic problems elsewhere, since it is a presumption that we act based on accurate information.

Consider, first, our knowledge of the efficacy of drug therapies. This is crucially dependent on patients actually taking their medication, from the clinical trials stage onwards; if the medicine has not been taken, then no pharmacological conclusions can be drawn from the absence of a therapeutic effect. So a process which cannot detect non-adherence is fundamentally flawed. Since both adherence and non-adherence may be partial rather than total [1], and will vary over time (defined within persistence), the problem deepens; at what level of adherence do we count a given patient as having taken the medicine optimally or not? There is no principled basis on which to say that taking 75% of one's doses is complying with therapy, but taking only half of them is not; nor, even taking the threshold to be arbitrary, is there any agreement as to the level it should be set at. Often the argument is made that adequate randomisation between arms of a study will mitigate against this confounder, but it stands to reason that if adherence in a gold standard randomised control trial cannot be accurately measured or ensured, the foundation of the results is somewhat shaky.

This is the case in clinical trials, but the same problem applies in trying to determine the efficacy of a given treatment for any individual patient; we cannot know if the therapy is having a positive pharmacological effect or not, if we do not know whether the therapy is actually being taken or not. And this raises a further epistemic problem for sleep medicine. Diagnosis and treatment of sleep disorders often proceeds by what is sometimes known as "empiric therapy". That is, the treatment process involves the initiation of new medicines, dose increases, etc. in a

systematic way, until an improvement is observed, and both treatment and diagnosis can be deemed successful. But testing drug therapies "by elimination" in this way cannot work if the treatment is not taken as directed; the medication has not *failed* to produce a satisfactory therapeutic pharmacological effect if it has not actually been taken. And since diagnosis and treatment are bound up together, so that the success of a treatment is our best clue to the accuracy of diagnosis, diagnostic reliability [13] for the field of sleep medicine as a whole is compromised.

Ethical Issues in Adherence to Therapy

At this point, the ethical implications of non-adherence start to bite. In any finitely-resourced healthcare system, expensive therapies must be allocated wisely. Correcting poor adherence is likely to achieve a better therapeutic outcome with lower cost compared to adding additional, potentially more expensive therapies [3,6,14]. Extensive evidence of this is seen in severe asthma [9,15].

One obvious, standard basis for allocating expensive therapies, accordingly, is to limit their prescription to those cases which have been deemed refractory following the failure of alternative, more well-known and often cheaper treatments [16]. But again, if a course of therapy has not been adhered to, it is inaccurate to characterise it as having "failed" in any relevant sense. Hence, being able to correctly identify the refractory patients from non-adherent patients is important to ensure resources are spent appropriately.

As an ethical basis for rationing therapy, then, this looks decidedly problematic. "Failure" of therapy due to non-adherence by patients may result in non-adherent patients gaining preferential access to more expensive treatments, ahead of similarly situated patients who might benefit at least equally from them, yet have seen smaller improvements by following their previous courses of treatment as directed. Potentially more seriously, deeming certain patients' sleep disorders to be refractory on this inadequate evidential basis, and devoting resources to expensive therapies as a result, involves an opportunity cost for users in all other areas of the healthcare system, to whose treatment the same resources might instead be assigned.

A rather different ethical concern with non-adherence concerns drug diversion - the transfer of any legally prescribed controlled substance from the individual for whom it was prescribed to another person for any illicit use. The typical drugs prescribed for sleep disorders – modafinil, methylphenidate, dexamphetamine, and sodium oxybate, for instance – have well-known illicit uses. So since there is evidence that such drugs are being dispensed to patients who do not go on to use them, there is a concern that they are being used by individuals other than the patient [17].

This is a problem in its own right; the over-prescription of drugs, which then go on to be abused by individuals other than the intended patient, has been a major driver of the opiate addiction epidemic in the US in recent decades. But attempts to address this sort of drug diversion, and its contribution to drug abuse, are likely only to exacerbate what we have identified as the basic issue from which most of the problems discussed here stem; the reluctance of patients to admit to their physicians that they have not adhered to the therapy prescribed, coupled with potentially creating fear of addiction to these therapies, further affecting adherence.

The fundamental moral problem posed by non-adherence to therapy, then, concerns the doctor-patient relationship, and the erosion of the patient's capacity to confide in their doctor and the doctors capacity to trust. The solution to this, and therefore a first step towards solving the other problems we have discussed here, seems – perhaps somewhat paradoxically – to lie in *de-moralising* that relationship. That is, a basis must be found for that relationship which treats non-adherence neither as a ground for blame on the doctor's side, nor for guilt on the patient's. Non-adherence to medicines should be an observation, not a criticism. And the key to that basis may be found in an ancient debate in the philosophy of action.

Akrasia and Adherence

According to Socrates, it is impossible for us to act in ways we know we shouldn't; to deliberately follow some course of action just is by definition to regard that as the best course of action to follow, all things considered [18,19]. But this has seemed false to many people since then; we are all, surely, familiar with the feeling of

knowing that we should really go for a walk, but nevertheless remaining on the couch, or knowing that we should get up in the morning, but hitting the snooze button on our alarm-clocks instead.

An early critic of this view was Aristotle, who drew a distinction between our reason and our appetites. When somebody is *eudaimon*, or flourishing, their reason and their appetites are aligned. But when their character as a practical agent has not been fully or properly formed, or is temporarily out of kilter, they may find their appetites and reason to pull in different directions; they may display *akrasia* or weakness of will (literally "incontinence"). That is, the majority of our failures to act as we should do not arise from a failure to understand or care sufficiently about what we ought to do; rather, they are failures of *action*, whereby we know perfectly well what we ought to do, but find ourselves unable to overcome our desires and inclinations in order to carry it out [20,21].

Understanding non-adherence to treatment as *akrasia* – *as* a failure of action – has the potential, we suggest, to re-orient the doctor-patient relationship in a less judgemental and therefore more open and honest way, thereby helping to remedy the problems we identified above. Two aspects in particular stand out as worthy of attention in this regard.

First, understanding non-adherence as an akratic failure of action means that it does not necessarily result from the patient lacking information. It should therefore come as little surprise that attempts to "educate" patients into adherence by providing more information about their treatment have often proved unsuccessful; the primary effect of such efforts may be to embarrass and alienate patients by making them feel ignorant or that the physician regards them in that way. In such circumstances, we cannot expect candour in response to queries about their adherence to therapy.

Second, understanding non-adherence as an akratic failure of action means that it does not result from a patient having the wrong values, or failing to regard their treatment as sufficiently important. Non-adherent patients are not, and should not feel themselves to be, bad or lazy people, or in possession of bad priorities. Again, a patient who feels that this is the conclusion to be drawn from their non-adherence, or at any rate that it is the conclusion their doctor *will* draw, is not likely to be

forthcoming about it when the doctor asks. It is perfectly reasonable that a patient takes their medicines as advised initially, but upon experiencing adverse effects or indeed, no effect, makes the *correct* decision to not take further doses. The failure here is in this decision not being communicated to the physician or indeed where this course of action is inappropriate, that the prescriber has not set realistic expectations for the patient with respect to its potential benefits and onset of action. We therefore propose that an honest admission of the action of non-adherence (by prescriber and patient) is the key to improving medicines use.

Conclusion

Recognising non-adherence as a common phenomenon in medicine allows the prescriber to better anticipate it and ultimately address it. Reliably identifying non-adherence can be difficult, as the objective measures we have are flawed, and unfortunately do not help us to understand the reasoning behind this behaviour. Our greatest hope is to appreciate the nature of the patient's decision-making when non-adherence occurs; using insights from the philosophy of action, we may be able to potentially ameliorate non-adherence by better understanding the reasons that patients fail to persist with courses of treatment. In this way, both the temptation to blame patients for non-adherence, and patients' own sense of being blamed or to blame, can be reduced, hopefully resulting in more honest and trusting patient-physician relationships, and a much more accurate sense of when non-adherence is occurring and why.

Key points:

* Non-adherence to therapy in sleep medicine creates epistemic problems regarding the efficacy of prescribed treatments, and the validity of disease-classification.

* These epistemic problems create ethical ones, concerning the rationing of therapy and potential drug diversion.

* Alleviating these problems requires getting patients to disclose non-compliance to their physicians, which involves a revised understanding of the patient-physician relationship.

* The key to such a revised understanding may lie in an ancient debate in the philosophy of action, concerning the ways that practical agents may fail to act in accordance with what they know to be the best course of action.

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