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Medication adherence as a learning process: insights from cognitive psychology

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ABSTRACT

Non-adherence to medications is one of the largest contributors to sub-optimal health outcomes. Many theories of adherence include a 'value–expectancy' component in which a patient decides to take a medication partly based on expectations about whether it is effective, necessary, and tolerable. We propose reconceptualising this common theme as a kind of 'causal learning' – the patient learns whether a medication is effective, necessary, and tolerable, from experience with the medication. We apply cognitive psychology theories of how people learn cause–effect relations to elaborate this causal-learning challenge. First, expectations and impressions about a medication and beliefs about how a medication works, such as delay of onset, can shape a patient's perceived experience with the medication. Second, beliefs about medications propagate both 'top-down' and 'bottom-up', from experiences with specific medications to general beliefs about medications and vice versa. Third, non-adherence can interfere with learning about a medication, because beliefs, adherence, and experience with a medication are connected in a cyclic learning problem. We propose that by conceptualising non-adherence as a causal-learning process, clinicians can more effectively address a patient's misconceptions and biases, helping the patient develop more accurate impressions of the medication.

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Introduction

Medication non-adherence costs the US more than $100 billion yearly and has taken on mounting policy importance with the introduction of financial incentives to improve adherence (Cutler & Everett, 2014; Osterberg & Blaschke, 2005). In addition, healthcare payers, providers, and patients are facing skyrocketing costs for new, remarkably effective medications for conditions from cancer (Gellad, 2014) to hepatitis C (Kabiri, Jazwinski, Roberts, Schaefer, & Chhatwal, 2014), highlighting the importance of better understanding how to improve adherence. Despite enormous effort in the past 50+ years to draw on social and behavioural theories to explain, predict, and improve adherence, interventions have generally yielded only modest improvements (Nieuwlaat et al., 2014).

Many existing theories of health behaviour in general posit that the following sorts of beliefs influence the decision to adhere to a medication regimen: whether adherence is believed to be successful in bringing about a desired outcome, whether adherence is believed to be necessary to achieve the goal, how quickly the outcome can be expected, and whether taking the medication is believed to

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cause other side-effects, to name a few. In this theoretical review, we provide a new framing for these common elements: we propose that all of these beliefs and thought processes can be understood as a process of *causal learning and reasoning*, reasoning about the cause–effect relations of taking a medication on various outcomes.

Importantly, a question not addressed by existing adherence models is where these beliefs come from. Though a patient may potentially develop beliefs about a medication from multiple sources such as friends and family, the internet, or a physician, we propose that one of the most psychologically salient sources of beliefs about a medication is a patient's own *experiences* with the medication. We propose that when a patient starts to take a new medication, the patient starts to learn about the causal properties of the medication (e.g., whether it is effective, how quickly it works, whether it is necessary, and whether it causes side-effects). This theoretical review focuses on the complex way in which a patient's experiences with a medication turn into beliefs and expectations about the medication. Furthermore, a patient's beliefs about a medication lead a patient to adhere or not, which in turn influences that patient's experiences with the medication. The complex nature of this cyclic process of experiences and beliefs means that false beliefs and misconceptions can lead to poor adherence, and vice versa. Understanding how patients learn about medications from experience may help identify ways to facilitate patients to develop more accurate beliefs about the true efficacy of the medication for them, and believing that the medication actually works may motivate patients to adhere better.

In order to unravel the complex relations between experiences and beliefs, we introduce theory and research from an area of cognitive psychology that studies how people learn and reason about cause–effect relations. Causal learning has so far not played a major role in helping to understand medication non-adherence. In particular, causal-learning research focuses on the information processing involved in how individuals learn from their experiences to make choices. In the sections below we integrate research on adherence and research from causal learning to (1) show the pervasive nature of causal reasoning when patients think about medications, and (2) demonstrate how understanding the complexity of the causal-learning task that patients face when starting a new medication can help explain why patients may develop misconceptions and false beliefs about medications, which can negatively impact adherence.

Common elements of predominant theories of adherence and health behaviour

The notion that patients think about the causal effects of taking medications and other health behaviours is not new. One of the most prevalent classes of theories of health behaviour are called value–expectancy theories, which include social cognitive theory (Bandura, 1977; McAlister, Perry, & Parcel, 2008), the health belief model (Champion & Skinner, 2008; Hochbaum, 1958; Rosenstock, 1974), the theory of planned behaviour (Ajzen, 1991), the common-sense model of self-regulation (Leventhal, Brissette, & Leventhal, 2003; Leventhal, Diefenbach, & Leventhal, 1992), and necessity–concerns framework (Horne, Weinman, & Hankins, 1999), among others. Value–expectancy theories assume that a patient's expectations about the likely outcomes of a behaviour will affect whether or not a patient will engage in the behaviour (e.g., take medication as prescribed).

On the surface, making a decision to take a medication based on an expectation of the outcome of the behaviour involves probabilistic causal reasoning: does this cause (a medicine) change the expected probability or severity of a relevant outcome? In philosophy this notion is termed 'difference-making'; whether the cause is expected to make a difference to the effect (Menzies, 2004), and there are numerous causal-learning theories that attempt to capture how people mentally compute whether a cause makes a difference (Hattori & Oaksford, 2007).

In addition, many of these theories of health behaviour propose that patients engage in additional types of causal reasoning about a health behaviour or medication. For example, Leventhal's Common Sense Model of Self-Regulation (Leventhal et al., 2003, 1992) proposes that patients conceptualise a disease in terms of the cause, timeline, consequences, and controllability of the disease, all of which

are causal. Horne et al.'s necessity–concerns framework posits that the more a medication is believed to be necessary to achieve a desirable health outcome, and the fewer concerns (side-effects) a patient expects the medication to cause, the more likely a patient will adhere to the medication regimen (Horne & Weinman, 1999; Horne et al., 2013). From a causal perspective, 'necessity' can be broken down into three parts: the patient must believe that (1) the outcome would be sufficiently unpleasant without the medication, (2) the medication has the capacity to produce the desired outcome, and (3) there are no other behaviours (e.g., other medications or lifestyle changes) that can produce the desired outcome. Laboratory experiments have shown that individuals' beliefs about sufficiency and necessity are important factors in causal learning and reasoning (Mayrhofer & Waldmann, 2015).

In sum, many of the key attributes of existing theories of health behaviour and adherence involve a patient reasoning about the cause–effect relations involved in their disease, treatment, and outcomes. Many of these existing theories also posit important roles for other factors such as self-efficacy, perceived barriers, personality traits, and so on. We do not deny the important roles of these other factors, but instead are attempting to elucidate the common thread of causal-reasoning cognitions that are a component of many of these theories.

One important remaining question is where a patient's causal beliefs about a disease and treatment originate. Leventhal's Common Sense Model of Self-Regulation (Leventhal et al., 2003, 1992) proposes that they come from a wide variety of sources including standard learning (e.g., reading in a book or online), stories from friends and family members about the disease and treatment, as well as prior experiences with medications. However, none of these theories go into the details of how experience with a medication turns into beliefs about the medication. This is the main focus of the rest of the article. This focus is also the reason for introducing theory from the subfield of cognitive psychology, which studies how people learn and reason about cause–effect relationships and form causal beliefs from direct experience.

Causal learning and reasoning

Causal reasoning is the sub-field of cognitive psychology pertaining to how people learn cause–effect beliefs through experience, and then use those beliefs for reasoning and making decisions, such as making predictions about the future and for choosing actions that have the highest likelihood of accomplishing a goal (Rottman & Hastie, 2014). Causal reasoning is a basic area of reasoning that applies to many domains of human endeavour, such as deciding how to behave in social settings based on one's cause–effect beliefs pertaining to how other people will react to one's actions, or how we reason about the cause–effect relations when trying to control a new mechanical device. In fact, one of the most common domains studied is reasoning about outcomes and side-effects of medications (e.g., Liljeholm & Cheng, 2007; Luhmann & Ahn, 2011; Rottman, 2016). We review three guiding principles of this research so that the application to adherence can be understood.

First, causal-reasoning research takes an information-processing approach to understanding how individuals build causal representations of the world and use them for reasoning and making decisions. For example, when deciding whether to take a medicine on a given day, a patient could assemble memories of prior experiences taking the medicine and not taking the medicine to form a judgement of the likelihood of obtaining a benefit from the medication and the likelihood of experiencing side-effects. This involves converting the remembered experiences into a judgement, analogous to running a simplified mental version of a statistical test to determine whether the medication has been effective. Understanding causal reasoning as information processing helps to explain how people are able to learn causal relations, and also when people will have difficulty accurately detecting causal relations.

Second, it is assumed that causal learning is a process that humans constantly engage in. Even non-human animals have remarkable abilities to learn the statistical associations between cues in the environment, actions, and outcomes (Rescorla & Wagner, 1972). Further, many of the sorts of decisions humans make, such as blaming a driver for an accident or predicting the outcome of a

sports game, can be viewed as different aspects of causal reasoning (Hastie, 2016). This ever-present aspect of causal learning implies that humans spontaneously track the relations between our actions (e.g., taking a medication or not) and the outcomes (e.g., experience a symptom or not) to make conclusions (e.g., whether the medication it is effective). Though humans cannot be expected to be perfect at causal learning, there is strong evidence of the basic causal-learning capacities (Rottman & Hastie, 2014; Sloman & Lagnado, 2015).

Third, a fundamental lesson from cognitive psychology is that learning involves a dynamic interplay of 'bottom-up' (experiences to beliefs) as well as 'top-down' (beliefs to experiences) processes. Applied to medications, experiences with a medication (e.g., symptom remission, side-effects) shape a patient's beliefs about the medication, and beliefs about the medication (e.g., whether the medication is thought to work) shape the patient's interpretations of symptoms and decisions about how to use the medication.

We propose conceptualising the problem of medication non-adherence as partly a learning phenomenon – the patient must learn whether the medication is working. If all medications provided clear benefits that outweigh risks and side-effects, presumably patients would be highly motivated to take them as prescribed. Unfortunately, many medications do not provide the patient with strong evidence that they are working. Understanding the challenges that patients face when learning about a medication can shed light on how a patient concludes whether a medication is effective and/or has side-effects and may suggest interventions for how physicians can help guide a patient so that their beliefs become more accurate.

Why learning about medications is so challenging for patients

When a patient attempts to learn about the causal properties of a medication (whether it works, how well, how quickly, whether it has side-effects), the patient is faced with a number of challenges arising from the fact that a patient's experience with a medication is essentially an informal version of an 'n-of-1' trial. One challenge is that a patient may desire to reach a conclusion about a medication from fairly little data. There are certain instances in which humans learn quickly and robustly from small samples; when a cause is quickly followed by its effect (Buehner, 2005). Thus, it is not surprising that we appreciate the benefits of pain relievers that work quickly, or even antibiotics that work within a day or two. However, many medications do not work quickly, making causal learning harder.

Second, when a patient starts a new medication, the evidence of whether the medication works involves a comparison of an outcome before vs. after the medication, and other factors, such as diet, age, air pollen count, change over time as well. In addition, patients are often started on multiple medications simultaneously, or asked to start a medication while simultaneously making a lifestyle change so that the two interventions are perfectly confounded. Indeed, patients are sometimes aware of these confounds, which leads to confusion for learning about the causal properties of a single medication (Siegel, Schrimshaw, & Dean, 1999).

Third, when starting a new medication an individual does not have a comparison group. For example, a patient with hypertension and cardiovascular risk might not perceive any day-to-day benefit from taking a statin (Rosenbaum, 2015). If a patient takes a statin for many years and does not experience a stroke or heart attack, it could be that the statin worked, or that it was not necessary.

Given these challenges, how can patients ever learn about their medicines? It is possible that patients often form incorrect beliefs about their medications. For example, patients may falsely believe that a medication causes a side-effect, even if the symptom was merely a coincidence. There are currently no metrics of how well patients actually learn about their medicines. But having an understanding of causal learning can potentially suggest ways that clinicians can facilitate accurate causal learning. We now review three key principles of how people learn causal relations that are particularly relevant to learning about medications.

Principle 1: beliefs shape the interpretation of experience

One of the challenges identified above is that patients have limited amounts of data from which to learn. However, there is a feature of how we learn that can speed up learning: prior beliefs. If a patient already has a prior expectation that a particular medication works well (e.g., perhaps based on stories recounted by friends and family members), when the patient starts to use the medication they will more quickly conclude that the medication indeed works. Likewise, if a patient has a prior belief that a medication has many side-effects, they will be more likely to conclude that it causes side-effects for themselves. In cognitive psychology this influence of prior beliefs on the interpretation of experience is called a 'top-down' effect (Griffiths & Tenenbaum, 2009; Waldmann, 1996).

Evidence of the influence of prior expectations on the interpretation of new experiences can be seen in medical studies and causal-reasoning studies. In medical studies, the placebo effect involves cases in which prior expectations overrule or distort the interpretation of efficacy (Benedetti, Enck, Frisaldi, & Schedlowski, 2014). (Here we are specifically talking about placebo effects in which the outcome is a subjective patient judgement like pain.) The fear that some physicians have of alerting patients to the possibility of rare side-effects of a medication can be viewed in a similar way of causing a 'nocebo' effect (Geddes, Cipriani, & Horne, 2014).

A similar effect is seen in basic causal-learning research. In one study participants pretended to be biologists trying to learn the relation between the presence vs. absence of a protein and length of a bacterium. There was a strong correlation between the two: usually when the protein was present, the bacterium was long, and when the protein was absent, the bacterium was short. There were also some instances in which the presence of the protein was paired with a medium-length bacterium. Afterwards, participants recalled how many times the protein was present and the bacterium was long. Because they formed an overall impression that the protein and bacterium height were causally related, they misremembered the medium-length bacteria as being long (Marsh & Ahn, 2009). In sum, causal beliefs shape the way that experiences are perceived, interpreted, and encoded in a 'top-down' fashion (see also Alloy & Tabachnik, 1984).

Beliefs can also get formed 'bottom-up' from first impressions with a medication. For example, suppose that a medication initially appears to have no effect on symptoms for one week, but during the second week the symptoms recede. After the first week, the patient may form a belief (bottom-up) that the medicine does not work, and then may perpetuate this belief (top-down) by attributing the subsequent improvement to the disease getting better on its own or inferring that another variable (e.g., new diet) was responsible. In causal-learning studies, beliefs formed from initial experiences can be perpetuated by influencing the interpretation of later experiences (Dennis & Ahn, 2001; Luhmann & Ahn, 2011).

Figure 1 shows a theoretical model of how initial beliefs get updated in learning. After each experience with the medication, the patient's beliefs about the medication get updated by incorporating both the prior beliefs and the new experience. However, because beliefs can alter the interpretation

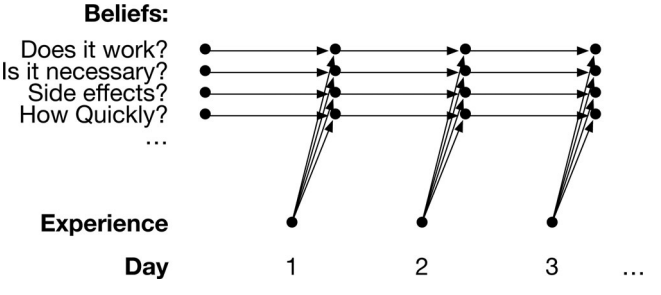

Figure 1. Partial model of causal learning about a medication.

of individual experiences, prior beliefs and beliefs formed at the beginning of learning can persist (the horizontal arrows).

In addition to beliefs about efficacy and side-effects, there are a variety of other beliefs that can be updated from experience such as how quickly a medication works. A number of causal-learning psychology experiments demonstrate that if an individual believes that a cause works quickly vs. works slowly, they parse the cause–effect evidence differently. Even if two people have the exact same set of experiences but different expectations of the timing of a cause–effect relation, the different expectations can lead to different conclusions about whether the cause influences the effect (Hagmayer & Waldmann, 2002; Marsh & Ahn, 2009). Additionally, the slower the cause–effect relation, the harder it is to detect that there actually is a relation (Shanks, Pearson, & Dickinson, 1989). This is particularly relevant to medication adherence because many medications take weeks before starting to work. Another belief is the curability/controllability of a disease. If a patient believes that the disease is unable to be cured but can be controlled, absence of a symptom could mean that the medication is working and necessary to keep the symptom in check. However, if a patient believes that the disease can be cured or go into remission, absence of a symptom could be interpreted as the medication no longer being necessary (Meyer, Leventhal, & Gutmann, 1985). Just like the other beliefs, beliefs about how quickly a medication works and about curability/controllability are likely learned both from a patient's direct experience with a medication (bottom-up), as well as shaped by prior beliefs (top-down).

The interpretation of new experiences is not always straightforward. For example, if a patient starts a new medication, and over time the patient's symptoms get worse, there are at least three interpretations that a patient may make: that the medication is (1) necessary and the dose should be increased to counter a worsening disease, (2) not working and that the disease is getting worse, or (3) causing these symptoms to get worse. Qualitative research has shown that patients often feel ambiguity when interpreting their symptoms (Morgan, 1996; Siegel et al., 1999). It is likely that prior beliefs about efficacy and necessity as well as beliefs about the natural progression of the disease could influence the interpretation a patient chooses. More broadly, the interpretation process based on prior beliefs is likely to be quite complicated.

This process of incorporating prior beliefs when interpreting one's own experience may seem like an irrational bias. However, incorporating prior beliefs when interpreting new experiences is actually a fundamental element of rational (Bayesian) learning and decision-making when experience is limited, noisy, and ambiguous, for both humans (Griffiths & Yuille, 2006; Pacer & Griffiths, 2011) and in artificial intelligence (Murphy, 2012). In fact, a similar rational learning argument has been made to explain placebo effects (Anchisi & Zanon, 2015). The key is that a learner should appropriately weight the prior beliefs and the incoming experience. When a patient is just starting out with a new medication, they have such little experience with a medication that their prior beliefs should have a large impact on their current expectations about the medication. As a patient uses the medication for longer and accumulates more experience, the role of prior beliefs should become smaller and smaller.

Because beliefs can influence the interpretation of new experiences, beliefs held before starting a medication and beliefs formed at the beginning of starting a new medication can have a long-lasting impact. This theory of learning suggests that interventions for improving the learning process should focus on developing accurate beliefs and expectations during the critical period when starting a new medication.

Principle 2: beliefs are hierarchical, and broad and specific beliefs interact

Another way to cope with limited, noisy, and ambiguous experiences for causal learning is to make use of 'hierarchical' beliefs (Griffiths & Tenenbaum, 2009; Hagmayer & Mayrhofer, 2013; Lucas & Griffiths, 2010; Tenenbaum, Kemp, Griffiths, & Goodman, 2011) about individual medications, classes of medications, as well as medications in general. Having hierarchical beliefs means that even if a

patient has no experience or beliefs about a particular medication, if they have had experiences and beliefs about another related medication, they can generalise these beliefs (to an extent), to the new medication, which can speed up learning.

This idea of a hierarchy of beliefs is similar to the theory behind the Beliefs about Medicines Questionnaire (BMQ; Horne et al., 1999; Horne & Weinman, 1999). The theory posits that patients have both specific and general beliefs: the specific beliefs are about necessity and concerns about side-effects for all the medications for a specific condition, and the general beliefs are about harmfulness and overuse of all medications. In one study, specific concern beliefs were correlated with general beliefs about the harms and overuse, and the specific beliefs were correlated with adherence. The authors proposed that the general beliefs may be the origin of the specific beliefs (Horne, Parham, Driscoll, & Robinson, 2009).

Based on formal computational hierarchical models of causal learning, we propose expanding upon the BMQ hierarchy in three different ways. First, in line with the previous section, we propose that causal learning is not just 'top-down' from general beliefs to specific beliefs, but also bottom-up from experience to beliefs. Second, we propose that in addition to forming beliefs about all medications in general (BMQ-general dimension) and about all the medications used for a particular condition (BMQ-specific dimension), that a patient will likely form beliefs about each individual medication. For example, one study found that among patients using combination antiretroviral therapy, 29% reported different rates of adherence to the different medications, which could be explained by having different beliefs about the medications (Gardner et al., 2008). More generally, this additional layer of beliefs about individual medications is needed to explain how a patient learns about individual medications from experience.

Third, in addition to beliefs about necessity and concerns, we propose that patients hold other beliefs, such as efficacy, that influence adherence (Campbell, Stang, & Barron, 2008; Lacey, Cate, & Broadway, 2009). Further, we propose that many of these beliefs could be held at multiple levels of the hierarchy. Concerns about side-effects, over-prescription, and efficacy beliefs could be held at all levels of the hierarchy. Beliefs about how quickly a medication works could be held for a specific medicine as well as a class of medications, though presumably patients understand that different classes work with different speeds.

This hierarchical theory can be visualised in Figure 2. Each of the curves represents a belief distribution (like a histogram) representing the confidence of a belief (Griffiths & Yuille, 2006). Similar hierarchies could be created for other beliefs aside from effectiveness.

The utility of this hierarchical framework is for thinking about how beliefs propagate across medications. For example, a negative belief about a medication may be due to a negative experience when starting the medication, a prior negative experience with a similar medication for the same condition, a negative experience with other unrelated medications, or an overall negative view towards medications in general. This hierarchy helps explain why propagating beliefs across different classes of medicines is an understandable, perhaps 'rational' process; in a probabilistic and uncertain world in which an individual only has limited experiences with a limited number of medications, it makes sense to import beliefs from other medications, especially other similar medications. Understanding these nuances of belief propagation may provide insight into how to address a patient's concerns. A clinician would likely use a different strategy to address specific concerns from experience with a particular medication vs. concerns about medications in general.

For example, if a patient has general concerns about medication side-effects, the goal of the physician would likely be to try to convince the patient to start to take the medication in the first place. Doing so may require explaining how this medication is different from other medications that the patient previously had a poor experience with (e.g., it is in a different therapeutic class), or involve starting the medication at a low dosage to try to avoid undesirable side-effects. In contrast, if a patient believes that a medication that they have been using is causing side-effects, the physician would need to address that particular experience with the medicine, for example, potentially explaining that some side-effects may be temporary, or that perhaps those perceived side-effects may be

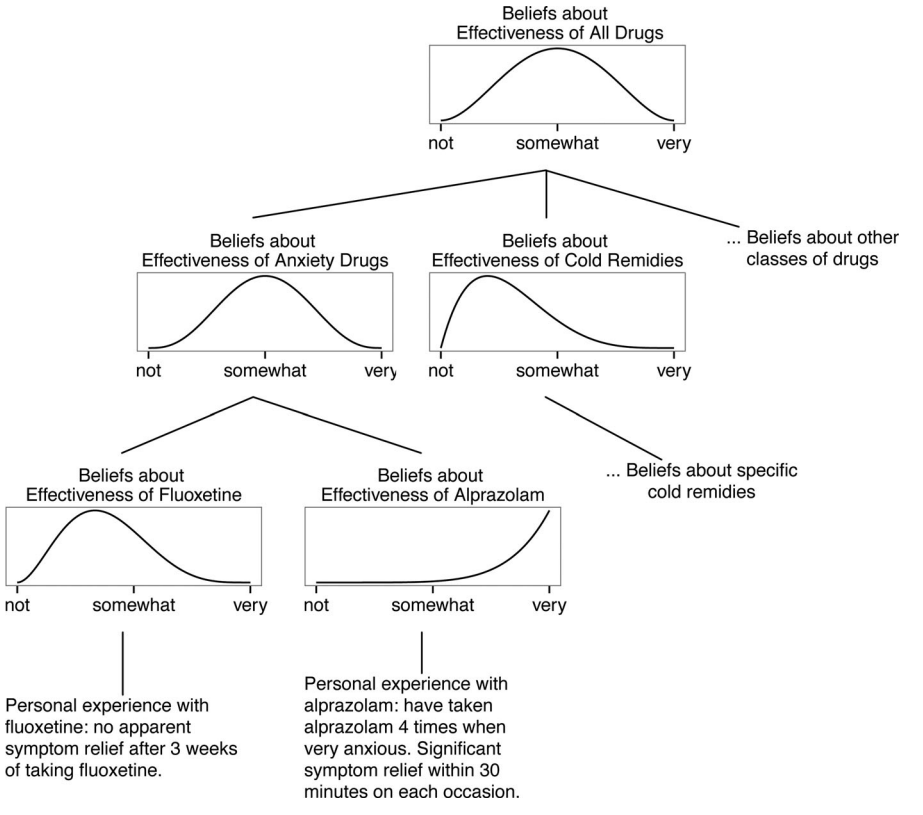

Figure 2. Hierarchy of beliefs about effectiveness of medications.

coincidences. Or if the physician believes that the side-effects are real, the physician may decide to instigate a conversation about other alternatives. In summary, these different concerns arising from direct experience with a medication vs. transferred experiences with other medications will likely arise at different times (before vs. after starting a medication), and will likely require different dialectical strategies.

Principle 3: choices and outcomes interact in complicated cyclic ways

So far this article has focused on the integration of personal experiences and beliefs about medications. In doing so, we have conveniently ignored another critical component to learning about medications that adds another layer of complexity – the decision whether or not to adhere to a medication regimen impacts the effectiveness and side-effects that are experienced. In Figure 3(a), this is

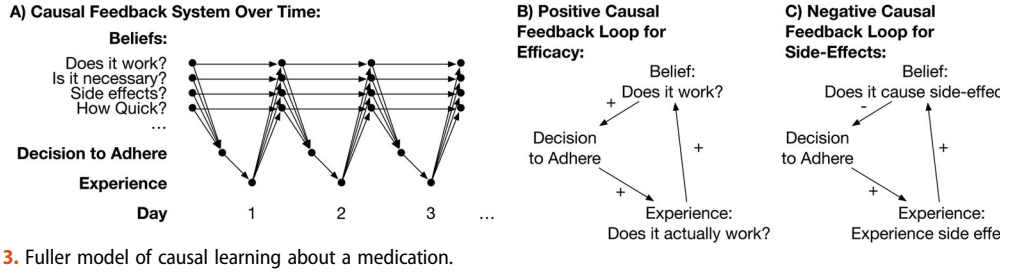

Figure 3. Fuller model of causal learning about a medication.

represented by the links from beliefs to adherence to experience. The decision to adhere could involve many different aspects such as (1) taking the medication, (2) at the right dosage, (3) at the right time, (4) and in the right way, such as with food. Altering any of these causal factors may change the effectiveness and side-effects that a patient will experience.

The fact that adherence determines a patient's experience with a medication sets up a complicated cyclic system. Consider efficacy beliefs (Figure 3(b)). Believing that a medication works would lead to better adherence, and better adherence would raise the probability that the medication would work to its full potential. Collectively, this should strengthen the patient's belief that the medication works. Alternatively, believing that the medication does not work would lead to worse adherence and worse experience, reinforcing the negative belief. In sum, adherence and efficacy beliefs typically form a 'positive feedback loop', more colloquially known as a 'vicious cycle' or a 'self-fulfilling prophecy'; good adherence can lead to better adherence, whereas poor adherence can lead to worse adherence (Figure 3(b)).

In contrast, adherence and side-effect beliefs typically form a 'negative feedback loop' (Figure 3(c)). When starting a medication, if a patient starts to experience side-effects, they may decide to take the medication less frequently to avoid the side-effects. In this negative feedback loop, good initial adherence can lead to worse adherence. (In rare instances, adherence and side-effects may sometimes work in a positive feedback loop. For example, because paroxetine has a short half-life and withdrawal effects, skipping doses can cause side-effects such as nausea, dizziness, and insomnia, which would encourage future adherence.)

In sum, this cyclic process between beliefs and adherence means that learning can be short-circuited by poor adherence. The simplest example is that a patient stops taking a medication before it has had time to start to work, or before they have time to become tolerant to side-effects. In fact, many patients 'experiment' with their medications in order to try to balance the benefits and the side-effects of the medications, which is sometimes called 'active non-adherence' (Dowell & Hudson, 1997; Pound et al., 2005). One study with hypertensive patients found that about 40% actively adjusted or omitted their medications based on perceived occurrence of side-effects, not liking drugs in general, and being asymptomatic or thinking that the medication was not necessary (Svensson, Kjellgren, Ahlner, & Saljo, 2000). Surprisingly, the authors concluded that patients who were non-adherent were more actively involved in their treatment than patients who were adherent. Patients who were non-adherent often had reasons for not taking the medication, whereas those who were adherent often did not have reasons for taking their medications aside from that it was what the doctor recommended. Another study on medication use in palliative care found that 44% took fewer medications than prescribed, most frequently because they thought that the medications were ineffective or that they were experiencing or anxious about possible side-effects, and 26% of patients used additional medications for symptom control (Zeppetella, 1999).

These studies demonstrate that patients understand that their adherence decisions influence their short-term experiences. The problem, however, is that short-term and long-term experiences may differ. A patient who is experiencing side-effects may stop taking a medication, and only much later learn the value of the medication as a disease worsens. For example, one study with HIV/AIDS patients found that sicker patients perceived a higher necessity of their medications and were more adherent (Gao, Nau, Rosenbluth, Scott, & Woodward, 2000). That is, they eventually did learn the value of the therapy, but only after experiencing the severity of the disease (and possibly harms of non-adherence). This example illustrates how learning feedback of efficacy, necessity, and side-effects can occur at different time scales and different stages in the disease process, which further complicates the processes represented in Figure 3.

In cognitive psychology, this problem of seeking a balance between costs and benefits by modifying a medication regimen is called an 'explore–exploit' dilemma (Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006). When deciding to take a medication on a given day (at the right time, right dose, etc.), the patient has two conflicting goals. The first is to produce the best outcome for the short term ('exploitation'), which is accomplished by taking the medication if and only if the patient currently

believes the benefits outweigh the harms. The second goal, 'exploration', is to figure out how well the medication works and the side-effect profile, which is useful for making a long-term decision to take the drug. Unfortunately, these two goals often conflict.

The explore–exploit dilemma can play out in many different ways. For medications that take time before becoming effective, skipping doses to avoid side-effects (exploit) would reduce the effectiveness of the medication, harming the patient's ability to figure out the true utility of the medication (explore). In contrast, for medications that work quickly (e.g., some antihistamines), skipping a dose can actually be useful because it provides a stark contrast of the benefits seen with medication vs. with no medication within a short period of time.

One problem in explore–exploit dilemmas is that it is often hard to understand why exploitation can be so harmful for exploration (Gureckis & Love, 2009). A recent causal-learning psychology study demonstrated that it is especially hard to learn about the efficacy of medications when the medication takes repeated usage before it works, and when the disease process naturally ebbs and flows, because it is hard to discriminate the efficacy of the medication from the natural phases of the disease (Rottman, 2016). Furthermore, in these situations, since natural phases of the disease can get interpreted as the medication working (or failing to work), exploiting the 'best' medication can result in especially poor learning about efficacy. An example of these problems is depression. Since it takes 6–8 weeks for most antidepressants to start to become effective, and because the disease ebbs and flows, it is hard to know if an improvement is due to the medicine or some other phase in the disease (Schedlowski, Enck, Rief, & Bingel, 2015).

In sum, adherence, experience, and beliefs form a cyclic learning problem. Furthermore, the desire to achieve the best outcome at a given point in time (exploitation) often impedes the goal of learning how well a medication works (exploration). Causal-learning studies that simulate how patients learn about particular medication-disease pairs may help to predict when patients will have difficulty learning that a medication is effective and how patients are likely to experiment with different sorts of medications. Alternatively, clinicians may be able to help patients navigate this cyclic learning process which could help them to see the value of a medication.

Implications for patient education: when and how?

This causal-learning perspective of adherence provides three main suggestions to help patients form accurate beliefs about their medications. First, because causal beliefs that a patient holds about a medication before starting the medication can influence the interpretation of a patient's experiences, screening early for negative outcome expectations and misconceptions would allow clinicians to address these attitudes before they distort learning (Marcum, Sevick, & Handler, 2013). Similarly, since a patient's early experiences with a medication can turn into beliefs that distort learning, we propose that early follow-up (e.g., Clifford, Barber, Elliott, Hartley, & Horne, 2006) to address concerns and reiterate realistic expectations could have long-lasting benefits. This suggestion aligns with research finding that the initial period when a patient is deciding whether to persist with a new medication is a critical time; during this time there is a substantial group of patients who skip doses or stop taking a medication entirely because of side-effects and other worries (Clifford, Barber, & Horne, 2008; Karter et al., 2009). It also appears that illness beliefs and representations may be a stronger determinant of adherence in acute than chronic diseases (Brandes & Mullan, 2014).

The second implication of this causal-learning theory is that it helps to clarify and distinguish different types of patient education that may be useful in different situations. The most important distinction is between the 'top-down' influence of prior beliefs (e.g., a patient does not want to take a medication because of a general concern about medications) vs. the 'bottom-up' influence of experiences (e.g., a patient does not want to take a medication because of a negative experience with that medication). These two situations will likely require different interventions, and we suggest future research into the most productive strategies to engage patients in conversations for these different situations. Future research may also find that other distinctions in beliefs (e.g., attitudes

towards all medications vs. beliefs about a particular class of medications in Figure 2) also benefit from different conversational strategies.

The third suggestion is to explain to patients what will happen if they do not adhere to the medication, both from an 'exploitation' (the short-term effects of the medication) and an 'exploration' (learning about the effectiveness of the medication) perspective. Since different medications work in many different ways (e.g., medications have different lengths of delay before starting to work, some diseases are easier or harder for the patient to detect improvement, and the efficacy of medications are influenced differently by poor adherence), it will be critical for healthcare providers to use their expert knowledge to explain to patients what they can expect to experience if they are adherent vs. non-adherent. But the basic point that must be communicated is that if they are non-adherent, they will never really know the extent to which the drug works. Motivational interviewing (Rollnick, Miller, & Butler, 2008) could potentially be used to help patients uncover their own conflicting goals (the goal to adhere to learn how well the medication works and the goal to not adhere to attempt to avoid side-effects), and hopefully to guide patients to decide on their own to temporarily withhold short-term goals and adhere to the medication regimen long enough to see if it works.[1]

Our suggestion that physicians may be able to help patients learn about their medications fits with a review of qualitative studies on adherence, which concluded in the following way:

> There is a need to accept that people are unlikely to stop resisting their medicines. Doctors could assist people in their lay evaluations of medicines by providing the necessary information, feedback and support … . However, doctors will need training and support to do this effectively. (Pound et al., 2005; see also Svensson et al., 2000)

We believe that this causal-learning perspective could help physicians and researchers conceptualise the learning problem that patients face so that they can better provide support for patients as they start a new medication.

Patients' experiences early in the course of medication treatment currently receive little attention in routine clinical practice, and it is unrealistic to assume that physicians alone can support these conversations with patients. Instead, we suggest that some of these conversations with patients can be initiated by non-physicians. In fact, although adherence interventions have suffered from null or modest effectiveness, some of the most successful interventions involved continued and early patient contact by non-physicians (Nieuwlaat et al., 2014).

Further, these conversations around the learning process would be facilitated by having patients self-monitor, record, and share their daily symptoms and medication-taking habits with their health professionals, rather than waiting weeks or months to follow up, at which point the patient would likely have well-entrenched beliefs. This communication can be facilitated by mobile-health technologies, enabling early, ongoing, and bidirectional communication to promote successful learning (Granger & Bosworth, 2011).

Patient self-management, personalised medicine, and patient-centred care

In addition to the 'adherence' paradigm of medication taking, this causal-learning framework also has implications for the 'self-management' paradigm in which the patient takes a more active role in decisions to manage their diseases (Bodenheimer, Lorig, Holman, & Grumbach, 2002; Pollock & Grime, 2000). If a patient decides to try a lifestyle change or an over-the-counter medication to treat a symptom, their perceptions of efficacy and side-effects govern their use of the therapy. Guiding the patient with realistic expectations of when to see a benefit, how best to use the therapy, and so on, could improve the patient's causal learning about the therapy by maximising the benefits, minimising the harms, and appropriately interpreting the experiences.

A related idea to self-management is using formal and carefully planned n-of-1 trials as a systematic way to determine an individual patient's response to therapy, a type of personalised medicine (Kravitz, Duan, & DEcIDE Methods Center N-of-1 Guidance Panel, 2014; Schork, 2015). (Here we are using personalised medicine in a somewhat different way than how it is often used – treating a

patient based on genetic information.) In standard clinical practice, the decision about whether a medication is working well enough to continue treatment is typically made through an informal judgement made by the patient (and or prescriber), often based on a patient's retrospective and unsystematic impression of efficacy and side-effects. This informal process is subject to many potential confounds (e.g., concluding that a medication works merely because a symptom has subsided) and sources of bias (e.g., initial prejudice for or against a treatment). In contrast, n-of-1 clinical studies involve systematically comparing two treatments or a treatment vs. a placebo by testing multiple phases of each treatment. Furthermore, n-of-1 studies often use the following design features to help ensure the validity of the design: wash-out periods after each treatment, repeated real-time (not retrospective) assessments of efficacy, randomised treatment sequences, and double-blinding (Kravitz et al., 2014).

The reason that n-of-1 trials are relevant to adherence is that, in a sense, n-of-1 trials are more formal and systematic versions of the 'experimenting' that patients already do to balance efficacy and side-effects (Dowell & Hudson, 1997; Pound et al., 2005). However, typically when patients 'experiment' with their medicines, it is viewed as non-adherent behaviour. In contrast, implementing a formalised n-of-1 study provides a mechanism for both the patient and prescriber to be more confident in the chosen medication, and also allows patients to more actively engage with the decision-making process, which in turn leads to better understanding of the disease and treatment, and a sense of empowerment (Nikles, Clavarino, & Del Mar, 2005). Causal reasoning is vital in carrying out n-of-1 trials; the prescriber must engage in causal reasoning to design the n-of-1 trial such as how long each treatment phase and wash-out period should be (Rottman, 2016), and both the patient and prescriber engage in causal reasoning when analysing the outcomes to determine the efficacy and side-effects of the medications.

Breadth of application and limitations of this causal-reasoning theory

We have cast this causal-reasoning approach to adherence as a cross-cutting factor that is common among many existing theories of behaviour and adherence. We also believe causal reasoning to be cross-cutting in another sense; even within individual models of adherence, causal reasoning touches upon many of the individual components. For example, consider the COM-B model (Jackson, Eliasson, Barber, & Weinman, 2014; Michie, van Stralen, & West, 2011), which posits three factors (capability, opportunity, and motivation) that influence behaviour. Causal reasoning is clearly influenced by the psychological components of capability such as comprehending the disease and treatment, as well as memory, judgement, thinking and planning abilities and constraints. The motivation factor is broken into reflective and automatic components. Causal reasoning is clearly a part of the reflective components of motivation such as outcome expectancies, perceptions of illness (e.g., the cause, chronic vs. acute nature) as well as beliefs about treatment (e.g., necessity, efficacy, concerns). The automatic component includes impulses arising from associative learning. Though the 'reasoning' aspects of causal reasoning (planning how to test causes, e.g., Rottman, 2016; controlling for alternative causes, e.g., Waldmann, 2000) go beyond associative learning, the process of learning whether a medicine reduces a symptom or causes a side-effect shares many similarities with standard theories of associative learning from experience (Pineño & Miller, 2007; Shanks & Dickinson, 1987). Opportunity includes all factors lying outside the individual that make performance of the behaviour possible or prompt it. Opportunity has the fewest connections with causal reasoning, but there are still some. For example, we have discussed how regimen complexity can make it difficult to assess which medicine(s) are responsible for an improvement in symptoms or side-effect, and the relationship between a healthcare professional and the patient can be vital for helping to facilitate accurate causal reasoning. Whether a patient has heard positive or negative stories about a medication could also be included in the social component of the opportunity factor.

Causal reasoning also cross-cuts the factors in another recent influential model of adherence, the Information – Motivation – Strategy model (DiMatteo, Haskard-Zolnierek, & Martin, 2012). Causal

reasoning is pervasive in the information and motivation factors, such as having accurate causal beliefs and sufficient knowledge of basic facts such as chronicity of a disease and how the therapy works, and having sufficient motivation to take the medication as prescribed, which we argue is largely based on a patient's own experiences with the medication. Causal reasoning is less related to the 'strategy' component, which is whether patients have a workable strategy for following treatment recommendations (e.g., overcoming practical barriers to treatment).

Even though we believe that causal-reasoning cuts across many of the factors that are typically included in models of adherence, there are plenty of other factors that play important roles in (non)adherence that are not related to causal reasoning. For example, developing strong habits for taking a medication so that the behaviour becomes routinised is especially important for minimising forgetting, which is crucial for long-term adherence. In contrast, causal reasoning about whether a medication works appears to have a larger impact on intentional non-adherence, such as intentionally skipping doses or modifying the treatment, and likely plays a larger role when first starting a medication (Phillips, Leventhal, & Leventhal, 2013). Other important factors to which we see fewer connections to causal reasoning include mood/emotion, social support, systems level barriers to access to medications, as well as other aspects of adherence outside a patient's volitional control.

Conclusion

The limited success to date of adherence improvement programmes may be explained in part by the inattention to adherence as a learning phenomenon. Social psychology has contributed a great deal to the understanding of adherence by focusing attention on patients' beliefs about medications. Further applying lessons from research on the cognitive psychology of causal learning may help clinicians guide patients towards more accurate beliefs of whether a medication is actually working, and, in turn, implement more patient-centred, and effective interventions.

Note

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