An Active Inference Approach to Dissecting Reasons for Non-Adherence to Antidepressants

Ryan Smith,[1] Sahib Khalsa,[1,2] Martin Paulus[1,2]

[1]Laureate Institute for Brain Research, Tulsa, OK

[2]University of Tulsa, Department of Community Medicine, Tulsa, OK

Corresponding Author Information:

Ryan Smith

Laureate Institute for Brain Research

6655 S Yale Ave, Tulsa, OK 74136, USA

Email: rsmith@laureateinstitute.org

Keywords: active inference; adherence; psychiatric treatment; computational psychiatry

Word count: (text: 3,964), (abstract: 248)

Figure count: 7

Table count: 3

Abstract

Background: Antidepressant medication adherence is among the most important problems in health care worldwide. Interventions designed to increase adherence have largely failed, pointing towards a critical need to better understand the underlying decision-making processes that contribute to adherence. A computational decision-making model that integrates empirical data with a fundamental action selection principle could be pragmatically useful in 1) making individual level predictions about adherence, and 2) providing an explanatory framework that improves our understanding of non-adherence.

Methods: Here we formulate a partially observable Markov decision process model based on the active inference framework that can simulate several processes that plausibly influence adherence decisions.

Results: Using model simulations of the day-to-day decisions to take a prescribed selective serotonin reuptake inhibitor (SSRI), we show that several distinct parameters in the model can influence adherence decisions in predictable ways. These parameters include differences in *policy depth* (i.e., how far into the future one considers when deciding), *beliefs about the predictability (stochasticity) of symptoms, beliefs about the magnitude and time course of symptom reductions and side effects,* and the *strength of medication-taking habits* that one has acquired.

Conclusions: Clarifying these influential factors will be an important first step toward empirically determining which are contributing to non-adherence to antidepressants in individual patients. The model can also be seamlessly extended to simulate adherence to other medications (by incorporating the known symptom reduction and side effect trajectories of those

medications), with the potential promise of identifying which medications may be best suited for different patients.

Introduction

The efficacy of medical treatment depends crucially on a patient's decision to adhere to the treatment prescribed. Unfortunately, the number of patients who choose to follow treatment recommendations are quite low – despite the fact that treatment would often lead to significant improvement in their quality of life (1). By some estimates nearly half of all prescribed medications are not taken and roughly 125,000 deaths each year are due to non-adherence; costs associated with non-adherence are also estimated to be between $100 and $300 billion annually (2). In the context of mental healthcare – which will be the focus of this paper – roughly one in five patients adhere to antidepressant medication treatment for more than four months (3), and the majority discontinue within the first 30 days (4). Low adherence rates also do not appear fully attributable to an objective lack of efficacy, as those who follow antidepressant treatment recommendations show lower levels of recurrence risk (5), cardiovascular mortality (6), overall mortality (7, 8) and lower suicide rates (9). Individuals who adhere to treatment also report greater perceived benefits and lower levels of medication-related concerns than those who do not adhere (1). Thus, it is somewhat perplexing that patients often choose not to adhere.

Major factors that can influence adherence decisions include patients' beliefs about medication and their personality attributes. For example, adherence to psychiatric interventions is lower in those with lower treatment expectancy (10) and in those who experience sexual side effects (11). These and other findings have led to the 'necessity-concerns framework' (12) which proposes that adherence decisions follow from weighing expected negative outcomes against beliefs about the necessity/efficacy of the treatment (13-18). Personality variables associated with greater adherence include higher *persistence* (19, 20), greater *self-efficacy* (21-23), lower *optimism* (24), greater *self-control* (25), and a greater *internal locus of control* (26) (27).

Habit formation – in which an action begins to occur more "automatically" (i.e., in the absence of explicitly expected future consequences) – may also be central to the development of stable health behaviors (28), an effect that could generalize to adherence behavior (29, 30). However, studies have found that the amount of time required to form strong habits is highly variable from one individual to another (e.g., 18 to 254 days in one study (31)). The processes that moderate habit formation time are therefore also highly relevant to understanding long-term adherence.

While several different interventions to promote adherence have been tested, involving educational (32, 33) counseling (34), and coaching (35) approaches, they have each shown little evidence of efficacy in randomized controlled trials (36). There is therefore a clear need to better understand the decision-making processes contributing to adherence behavior. Such processes, if better characterized, could possibly help inform more targeted interventions as well as inspire the creation of better measures for predicting adherence.

In this manuscript our goal is to construct a computational model that can generate decisions to adhere or not adhere, and that provides a detailed characterization of several different probabilistic beliefs and related inference processes that plausibly contribute to these decisions. Computational approaches, and those associated with computational psychiatry in particular (37-40), have gained prominence in recent years due in part to their potential to characterize such processes in a quantitative manner and to illustrate the way a number of underlying processes central to any decision-making system can contribute to maladaptive perception and behavior.

In what follows we introduce a specific computational model of antidepressant medication adherence, based on the active inference framework (41). The development of such a model may be crucial in clarifying the way that individual differences in computational processes can

arbitrate between adherence and non-adherence in individual patients. We will focus on the initial decision to adhere over the first 12 weeks of treatment, in which symptoms typically decline and stabilize (42) and in which side effects first appear and subsequently reduce somewhat in severity (43). We will then simulate processes that may moderate the speed with which individuals can develop a strong medication-taking habit after their initial decision to adhere.

An active inference model of adherence

According to the Active Inference model used here (41), the brain embodies a generative model that represents different possible states of the world and continuously generates predictions about the observations/outcomes it will receive from the internal/external environment if its beliefs are accurate. It then uses subsequent observations to update the model and to generate sequences of actions (policies) that are expected to minimize uncertainty and lead to the most preferred outcomes. This type of model (see figure 1 for more details) is formally known as a partially observable Markov decision process (MDP) and provides a particularly useful heuristic framework to examine alterations in decision processes due to altered affect-driven belief systems (44, 45). The formal basis for Active Inference has been thoroughly detailed elsewhere (41, 46-49), and the interested reader is referred there for a full mathematical treatment.

In our model, the policy to adhere or cease adhering on (any day during) each of 12 weeks of treatment (13 policies total, formally modeled as one choice per week) is based on initial predictions about how observed depressive symptom severity (from 0-10) and side effect severity (from 0-3) will change over time given each possible choice, and on how these

expectations are subsequently updated when actual changes in symptoms and side effects are observed. The possible states in our model correspond to beliefs about "perceived quality of life" (which predict different combinations of observed depressive symptom and side effect levels), and beliefs about whether or not one is currently choosing to adhere (which predict different patterns of change over time in depressive symptom and side effect levels).

One must also specify several matrices in an MDP that define the probabilistic relationships between each of these variables; these include a matrix encoding the relationships between *states and observations* (**A** matrix), how *states are expected to evolve over time* (**B** matrix), the relative *preference for some observations* over others (**C** matrix), *expectations about the initial states* one will start out in (**D** matrix), and *prior expectations about which actions one is most likely to choose* in general (**E** matrix). For more detail about each of these variables and matrices, see table 1 and figure 1.

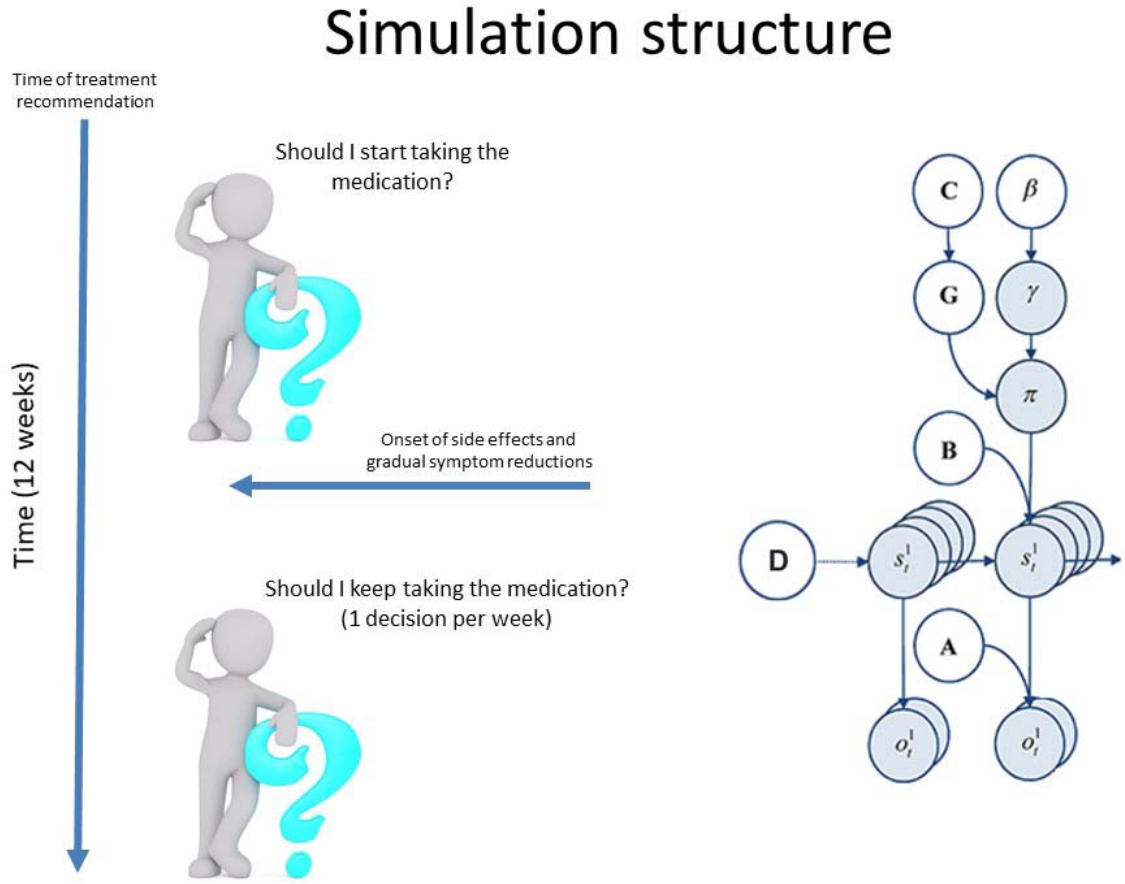


Figure 1. Illustration of the Markov decision process formulation of active inference used in the simulations described in this paper. The generative model is here depicted graphically on the right, such that arrows indicate dependencies between variables. Here observations (*o*) depend on hidden states (*s*), where this relationship is specified by the **A** matrix, and those states depend on both previous states (as specified by the **B** matrix, or the initial states specified by the **D** matrix) and the sequences of actions/policies (π) selected by the agent. The probability of selecting a particular policy in turn depends on the expected free energy (**G**) of each policy with respect to the prior preferences (**C**) of the agent. The degree to which expected free energy influences policy selection is also modulated by a prior policy precision parameter (γ), which is in turn dependent on beta (β) – where higher values of beta promote lower confidence in policy selection (i.e., less influence of the differences in expected free energy across policies). For more details regarding the associated mathematics, see (46, 50). In our model, the observations were depression symptom levels and antidepressant side effects, the hidden states included beliefs about progress in treatment over time (i.e., improvements in quality of life) and beliefs about adherence decisions, and the policies included the choice to adhere or cease adherence at each week over 12 weeks of treatment (e.g., choosing to discontinue on a Wednesday vs. a Saturday of a given week was treated as the same choice in the model; as described in the main text, this modeling choice allowed the integration of week by week empirical data on symptom and side effect trajectories on antidepressants). As depicted on the left, our simulations began at "week 0" when treatment was initially recommended; the simulated patient then chose whether or not to adhere to treatment based on their beliefs about the way that symptoms and side effects would change over time if they did vs. did not adhere. Preferences were

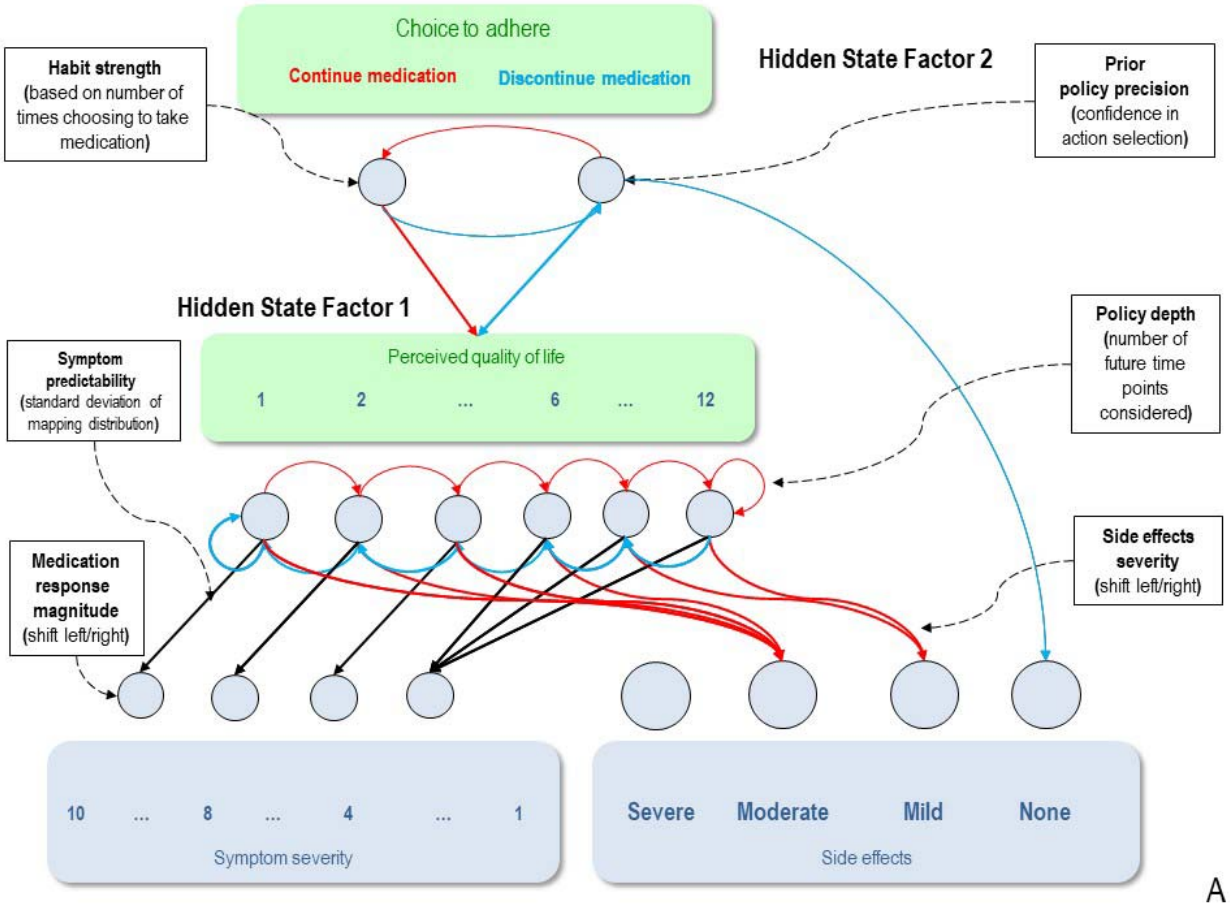
set such that the agent has stronger and stronger preferences to observe lower and lower symptom levels as well as lower and lower side effect levels.

In our model, the **A**-matrix was constructed such that steadily lowering (but fluctuating) symptom levels were generated for each week the agent continued to take the medication (based on the dose response time courses empirically characterized in a mega analysis of three SSRIs; (42)). Specifically, Gaussian distributions were specified over a symptom severity scale from 0 to 10, with empirically based means that probabilistically decreased from baseline levels over the 1st 6 weeks of treatment and then remained somewhat stable thereafter (i.e., depending on the standard deviations set for these distributions). The means were: 9.36, 8.04, 6.91, 5.94, 5.10, 4.38, 3.77. The medication taking action also generated moderate side effect levels in the first six weeks and mild side effect levels from weeks 7 to 12 (broadly based on the empirical antidepressant side effect time courses characterized in (43)). In contrast, the choice to cease taking the medication led to the cessation of side effects and a gradual return to baseline symptom levels.

The **B**-matrix was constructed so that agent controlled the transition from choosing to take the medication to choosing to cease the medication at each week (i.e., if two individuals ceased taking the medication on different days during the same week, these were formally treated as the same choice). Simultaneously, each action was associated with transitions toward increasing or decreasing perceived quality of life levels, respectively. The **C**-matrix was constructed such that the agent preferred the lowest symptom levels most (magnitudes from 0-10) and the lowest side effect severity most (magnitudes: 0, 2, 4, 6). The **D**-matrix was constructed such that the agent always began in an initial state of being "undecided" about choosing to adhere or not, and always began in an initial state of being at the lowest perceived

quality of life. The **E**-matrix was initially set such that the agent had no bias (habit) for choosing to adhere or not adhere.

The parameters that characterize individual differences in our model are described in table 2. These correspond to differences in (beliefs about) the predictability and magnitude of changes in symptoms and side effects, how far into the future one considers when making decisions (policy depth), confidence in the consequences of choosing different actions (prior policy precision), and the strength of medication-taking habits.



A

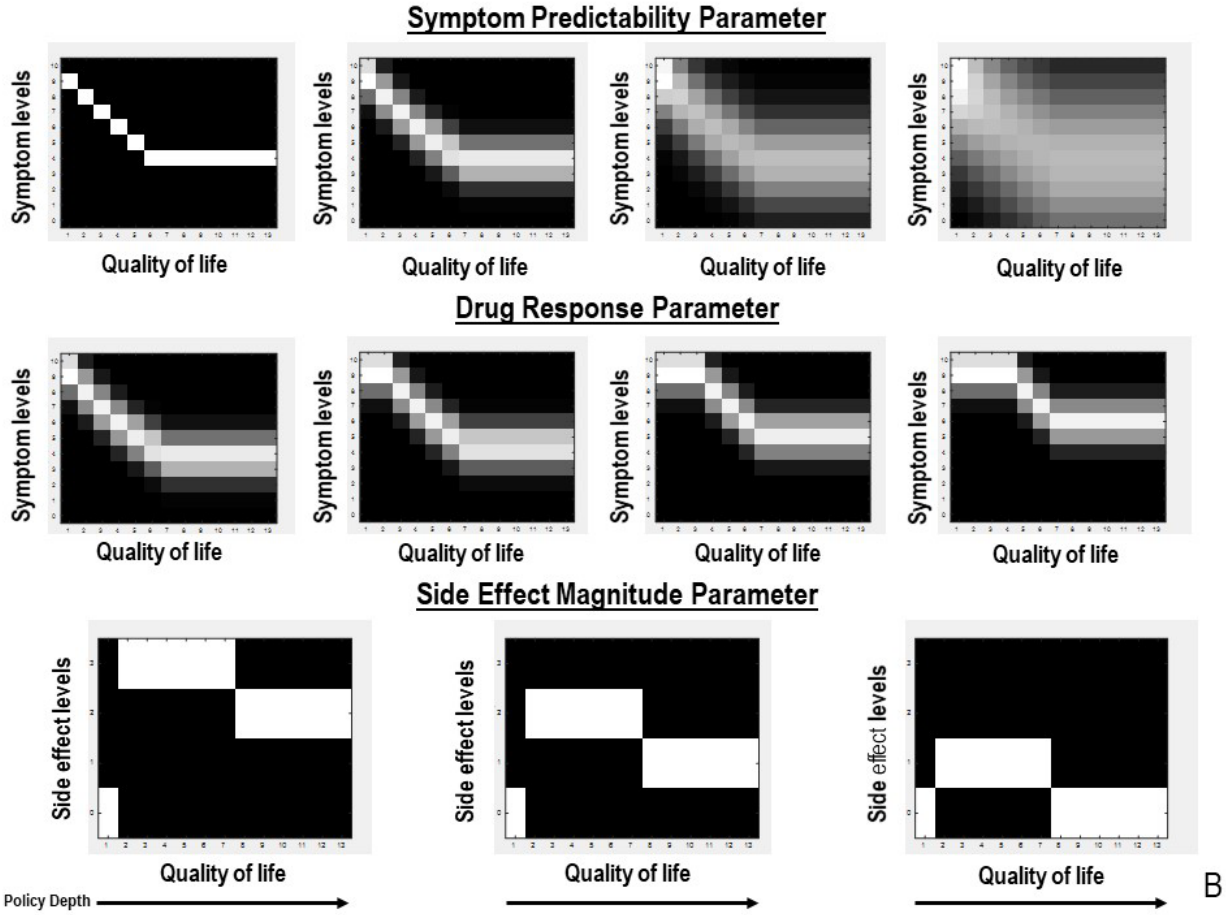


Figure 2. (A) Displays the levels of hidden state factor 1 and 2 (treatment progress and adherence decisions) and their mapping to different lower-level representations of symptom levels and side effect severity (here modelled as outcomes). Each combination of levels in the two hidden state factors generated different observation patterns and state transitions with different probabilities. Red arrows correspond to the observations (and transitions) generated when the simulated patient chooses to continue medication, whereas blue arrows correspond to the observations (and transitions) generated when the patient chooses to discontinue medication (see text for details). Black arrows correspond to observations generated by hidden states that do not depend on the selection of one policy vs. another. Each of the six parameters in the model are also illustrated with a brief description (and described in the text in more detail). For example, symptom predictability was modulated by reducing the precision of the mapping from hidden state levels to symptom severity observations. Response magnitude was modulated by shifting the observable symptom severities toward lower or higher levels. Side effect severity was modulated by shifting the observable side effect levels to higher or lower values. For example, while in the figure it shows that moderate side effects are generated in the first six weeks of treatment and mild side effects are observed thereafter, this could be shifted such that they instead transition from severe to moderate, or from mild to none. See the text and tables for a thorough description of the other parameters. (B) Displays the **A**-matrices encoding the state-observation mappings under different parameter values (i.e., lighter colors indicate higher probabilities). (Top row) The precision of the first matrix (i.e., encoding beliefs about how precisely different "perceived quality of life levels" – corresponding to the amount of time on the medication – will lead to different observed symptom levels) could be adjusted via specifying the standard deviation of an associated Gaussian probability density function (SDs = 0.1, 1, 2, and 4 are shown here from left to right). (Middle row) Medication response magnitude could be modulated from (from left to right) strong, moderate, weak, and very weak responses, corresponding to

incremental shifts upward and to the right in the same matrix. (Bottom row) The second matrix (i.e., encoding beliefs about how taking the medication will generate different side effect severities over time) could also be modulated to simulate the magnitude of side effect responses. From left to right, the patient either initially experience severe side effects that eventually settled at moderate levels, initially moderate levels of that eventually settled at mild levels, or initially mild levels that eventually resolved. The arrows indicating policy depth signify that those with greater policy depths will consider more distant predicted observations in decision-making.

Simulating individual differences in adherence

Initial simulations

The left panel of figure 3 illustrates an example simulation under one set of parameter values, in which policy depth was at its maximum value of 12, symptom predictability was high (SD = 0.01), symptom reductions were high (i.e., the agent was a "strong responder" to the drug), side effects were mild, policy precision was high ($\beta = 1$), and no medication-taking habit had been formed (the **E**-matrix distribution was flat over all policies). As can be seen, the agent chose to adhere and observed steady symptom reductions and some initial mild side effects that resolved after the first six weeks. The middle panel of figure 3 illustrates another example simulation in which symptom predictability was reduced (SD = 2) and side effects were severe. In this case, the agent chose not to adhere. In these simulations, the agent's expectations were consistent with its subsequent observations. The right panel of figure 3 illustrates a third example simulation in which the agent believed symptom predictability was higher than it really was (SD = 1 vs. 2) and side effects and symptom reductions were moderate (which the agent expected). In this case, the agent took the medication the first week, but then ceased taking the medication after observing an unexpected increase in symptom levels during the second week.

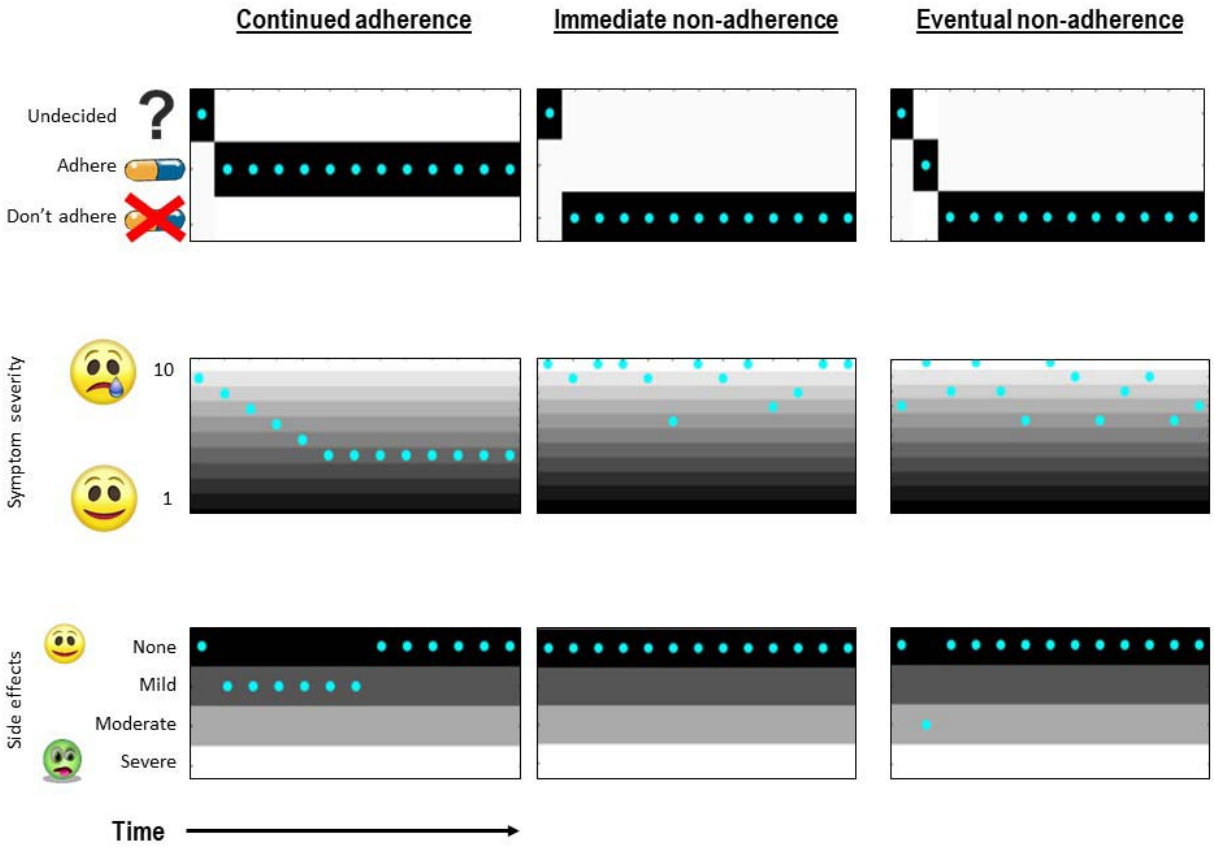


Figure 3. Example trials displaying different adherence decisions under different parameter values. In the top plots, cyan dots indicate the true action taken, and darker colors indicate higher levels of confidence in one action over others. In the middle and bottom plots, cyan does indicate observations, whereas darker colors indicate more strongly preferred observations. The top plots illustrate the choice to adhere or not adhere at each of the 12 weeks, the middle plots display observed symptoms over time with severities from 10 to 1, and the bottom plots illustrate observed side effects from mild to severe. Under the parameter values used in the left simulation, including mild side effects, strong symptom reductions, and high symptom predictability, the agent chose to adhere. Under the parameter values used in the middle simulation, in which symptom predictability was low and side effects were severe, the agent chose not to adhere – leading to an absence of side effects and symptoms continuing to fluctuate around baseline levels. Under the parameter values used in the right simulation, in which the agent expected symptoms to be more predictable than they actually were, the agent initially chooses to adhere but then stops when it observes an unexpected fluctuation upward and symptom intensity and a moderate increase in side effects. After ceasing medication, side effects resolve and symptoms continue to fluctuate around baseline levels. See the main text for more details about the parameter manipulations in each simulation.

Parameter interactions in the context of accurate expectations

To better characterize this parameter space, we repeated the simulations above at each of many combinations of parameter values. Figure 4 illustrates two example plots from part of this parameter space where the agent had accurate expectations, in which medication response magnitude and side effect severity were fixed at moderate levels. Here, the x-axis in each plot corresponds to symptom predictability (from low to high: i.e., SDs from 4 to 0.1), whereas the y-axis corresponds to policy depth (from 2 to 12 weeks). The plot on the left corresponds to an agent with low policy precision ($\boldsymbol{\beta}$ = 10), whereas the plot on the right corresponds to an agent with high policy precision ($\boldsymbol{\beta}$ = 1). Black squares in these plots correspond to agents that remained adherent all the way into week 12, whereas white squares indicate agents that ceased adherence prior to week 12. As can be seen, there is a clear boundary in which, below a certain policy depth and level of symptom predictability, adherence behavior ceases. Interestingly, adherence behavior increases across the space when policy precision is low. This suggests that, when one is not confident in policy selection (it is less clear that one policy will produce more preferred observations than others), one is more likely to adhere in an "exploratory" manner (e.g., "I don't think this will work, but who knows?").

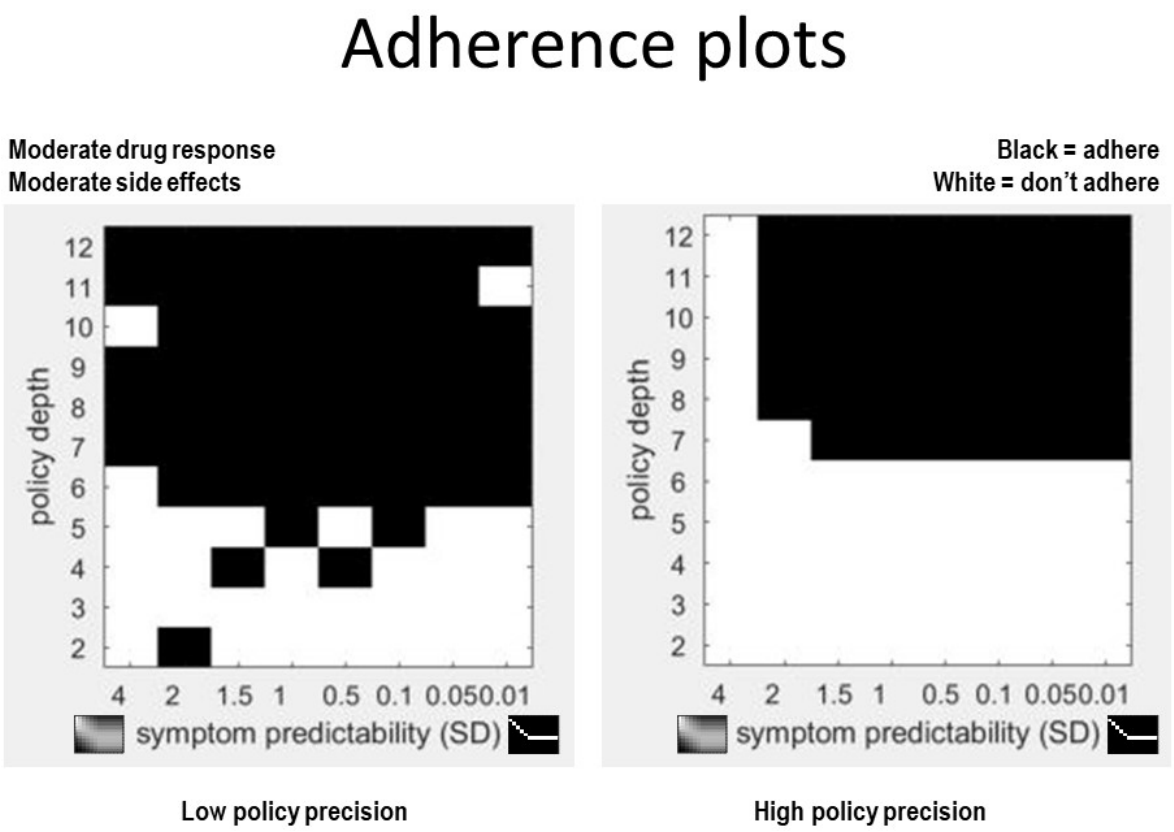


Figure 4. Two example plots from a larger parameter space with dimensions corresponding to different values for policy depth, symptom predictability, drug response magnitude, side effect severity, and policy precision. In these two plots the agent had accurate expectations about what it would observe under different policies, and medication response magnitude and side effect severity were fixed at moderate levels. The x-axis in each plot corresponds to symptom predictability (from low to high: i.e., SDs from 4 to 0.1), whereas the y-axis corresponds to policy depth (from 2 to 12 weeks). The plot on the left corresponds to an agent with low policy precision (β = 10), whereas the plot on the right corresponds to an agent with high policy precision (β = 1). Black squares in these plots correspond to agents that remained adherent all the way into week 12, whereas white squares indicate agents that ceased adherence prior to week 12. The main text for interpretation.

Figure 5 provides a more complete depiction of this parameter space under different levels of medication response magnitudes (larger x-axis across plots, from very weak to strong response) and side effect severities (larger y-axis across plots, from low to high severity). As can be seen, under high side effect severity and low response magnitude, adherence does not occur

no matter the policy depth or symptom predictability (upper left plot), whereas adherence occurs fairly broadly when side effects are low and response magnitude is high (bottom left plot).

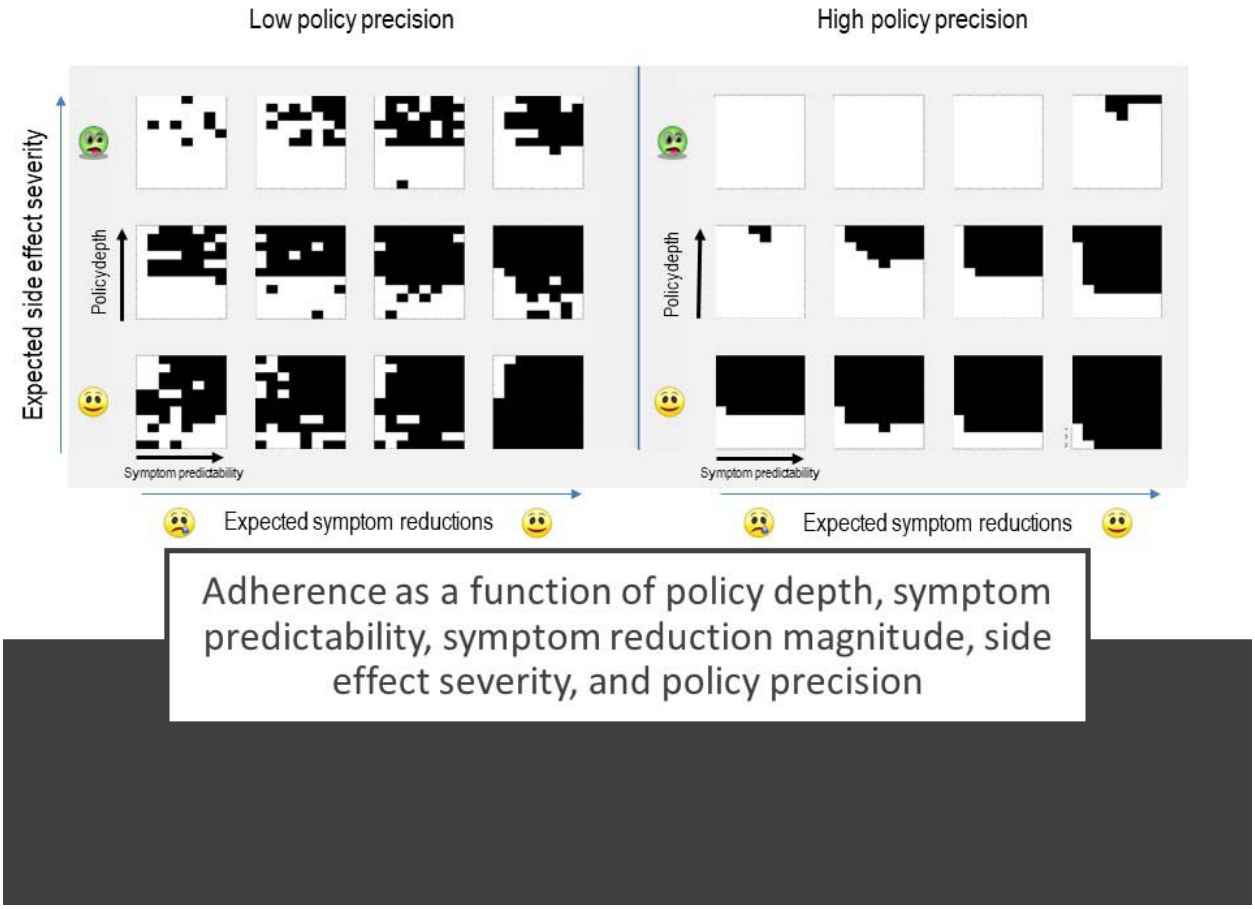
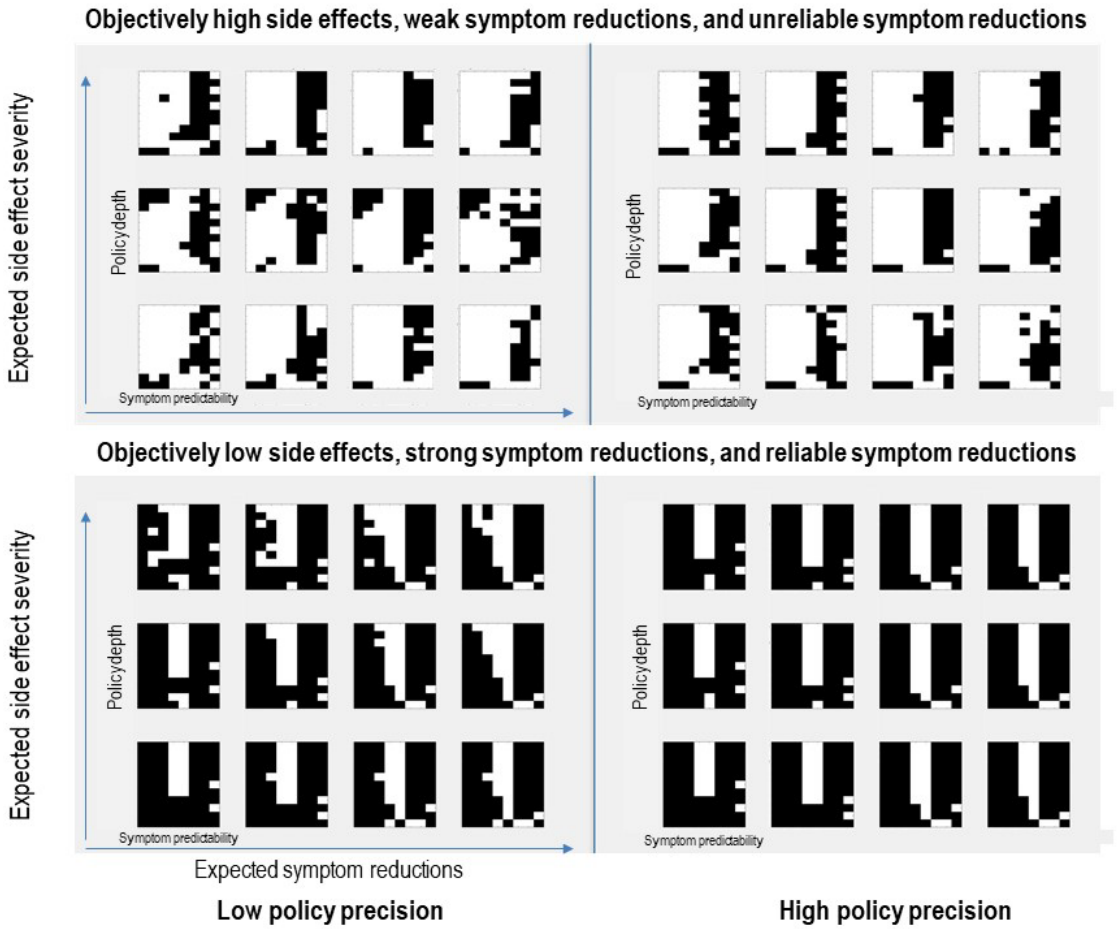


Figure 5. A more complete depiction the parameter space illustrated in figure 4 including different levels of medication response magnitudes (larger x-axis across plots, from very weak to strong response) and side effect severities (larger y-axis across plots, from low to high severity). See main text for interpretation.

Parameter interactions in the context of inaccurate expectations

Crucially, in the previous simulations it was assumed that the agent's beliefs about the effects of medication were accurate. However, a patient's beliefs need not match reality. As

such, we then dissociated the agent's beliefs from the statistics of subsequent observations to see if the agent being surprised would influence adherence in interesting ways. Figure 6 depicts a number of illustrative locations in this space. The x-axis in each graph corresponds to subjective beliefs about symptom predictability, where actual symptom predictability instead varies between groups of plots (see figure legend for more details). Similarly, beliefs about drug response magnitude and side effect severity are now depicted across plots within each group of plots, whereas actual drug response magnitude and side effect severity vary across groups of plots.



A

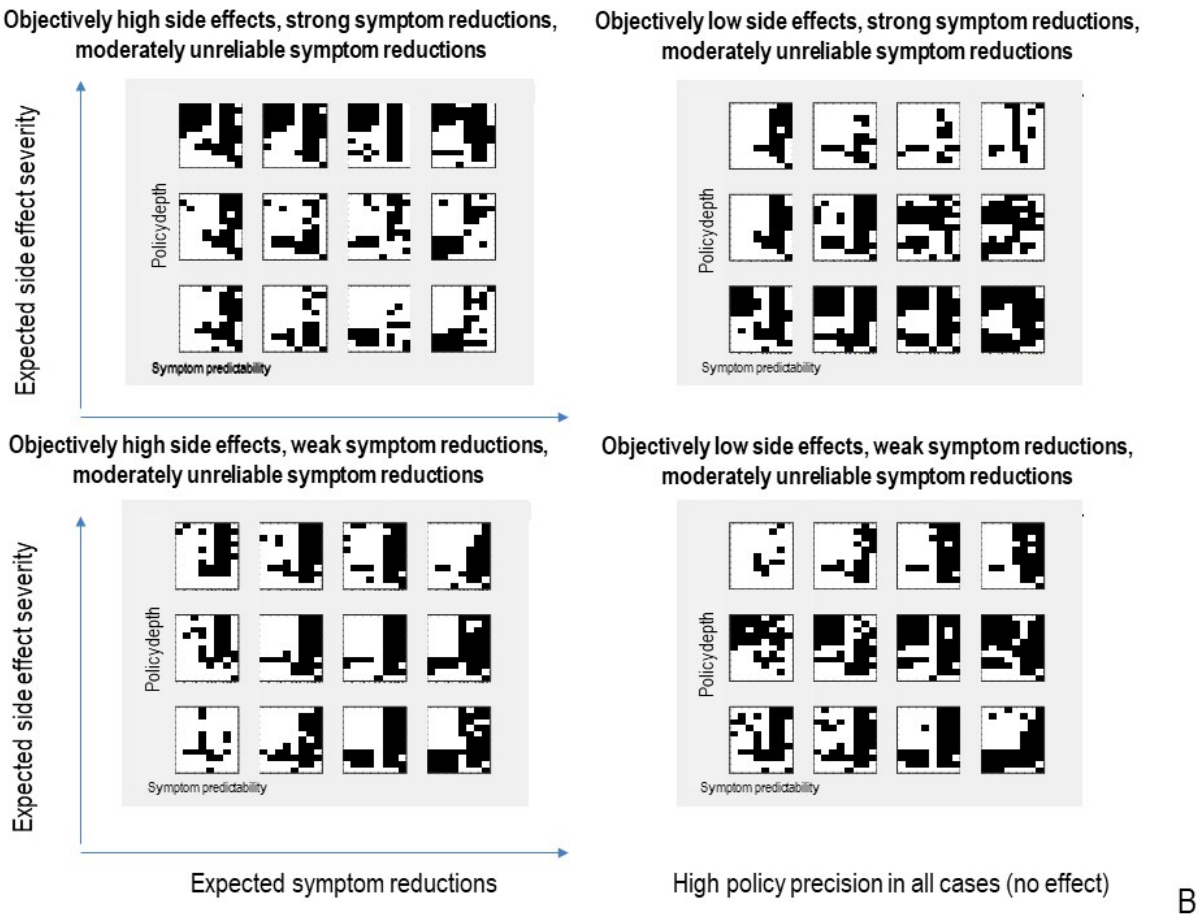


Figure 6. A depiction of several locations within a higher dimensional parameter space than that shown in figures 4 and 5, in which the agent's beliefs about symptom predictability, drug response magnitude, and side effect severity could differ from the true values generating their observations. Here the x-axis within each plot corresponds to the agent's beliefs about symptom predictability while the y-axis within each plot still corresponds to policy depth. The larger x-and y-axes across each group of plots now corresponds to the agent's beliefs about drug response magnitude and side effect severity, respectively. Each group of plots in turn corresponds to different combinations of the actual parameter values generating the agent's observations. The top and bottom plots in panel A illustrate the influence of very low (SD = 4) vs. very high (SD = 0.01). The 4 plots in panel B instead illustrate the influence of different combinations of objectively high/low side effect severities and high/low drug response magnitudes under cases of moderately unreliable symptom reductions (SD = 0.5). See text for interpretations.

One result is that, when observed symptom reductions are highly unreliable/noisy, the agent only remained adherent if her prior expectations very precisely predicted that they would be reliable. When observed symptom reductions were instead highly consistent/reliable, the

agent surprisingly also chose to adhere when she expected symptom reductions to be highly unreliable. Thorough inspections of the parameter space confirmed that, in these cases of highly reliable or unreliable symptom reductions, there was little influence of policy precision, drug response magnitude, or side effect severity. Other interesting results were observable in cases of objectively moderate levels of symptom reduction reliability. For example, there appears to be a general effect in which adherence was higher when expectations about side effects matched the actual side effects observed. This effect was more pronounced in the case of objectively strong drug responses; in the case of objectively weak drug responses and severe side effects, adherence levels also became more dependent on the expected reliability of symptom reductions. In cases of objectively low side effects, adherence went up in general, most notably in cases of high policy depth and the belief that symptom reductions would be unreliable (unless expected side effects were severe).

The general finding that adherence is higher when expected observations about side effects are confirmed appears sensible, in that, if one initially chose to "try out" adherence based on one's expectations, non-preferred surprising observations would be more likely to "change one's mind" later. The finding that, in the context of objectively reliable symptom reductions, adherence occurs at low but not intermediate levels of expected symptom predictability is initially more surprising. However, when symptoms are expected to fluctuate very unreliably, it makes sense retrospectively that being "pleasantly surprised" that observations are more reliable than expected would promote adherence. In contrast, if one initially expects moderate predictability, the level of surprise may not be sufficient to change one's mind. Finally, it is fairly intuitive that, in the face of highly fluctuating symptoms, adherence would require a strong

counteracting belief that they would still be reliable at future time points (e.g., "it's been a bumpy ride to start, but I think things are going to stabilize soon").

Parameter interactions in the context of habit formation

To investigate why some individuals take much longer to form strong habits than others (as reviewed in the introduction), we ran a final set of simulations in which we manipulated the strength of our simulated agent's habit to take medication. We manipulated the **E**-matrix in the model so as to simulate the effect of an agent having observed herself take medication different numbers of times (i.e., 1, 15, 30, and 60 previous medication-taking decisions). We also gave the agent a policy depth of 1, such that she was not forward-looking beyond the immediate expected consequences of adhering. As can be seen in figure 7, different simulated agents begin to adhere habitually after different lengths of time depending on several of the other parameter values manipulated in the simulations described previously. Longer time periods of previous adherence lead to habitual adherence. Habits also took longer to develop when expected drug responses were low and unpredictable, and when expected side effect severity was high (i.e., the medication-taking "impulse" less effectively competed against explicit planning when strongly non-preferred or unpredictable outcomes were expected to occur immediately). Low policy precision also led to much faster habit formation. Psychologically, this might be interpreted as indicating an interesting (and somewhat paradoxical) predicted effect. That is, in the context of higher side effects and lower drug responses, individuals who are less confident in decision-making should actually be more likely to adhere long-term than those who confidently predict at treatment onset that the drug will not be very helpful.

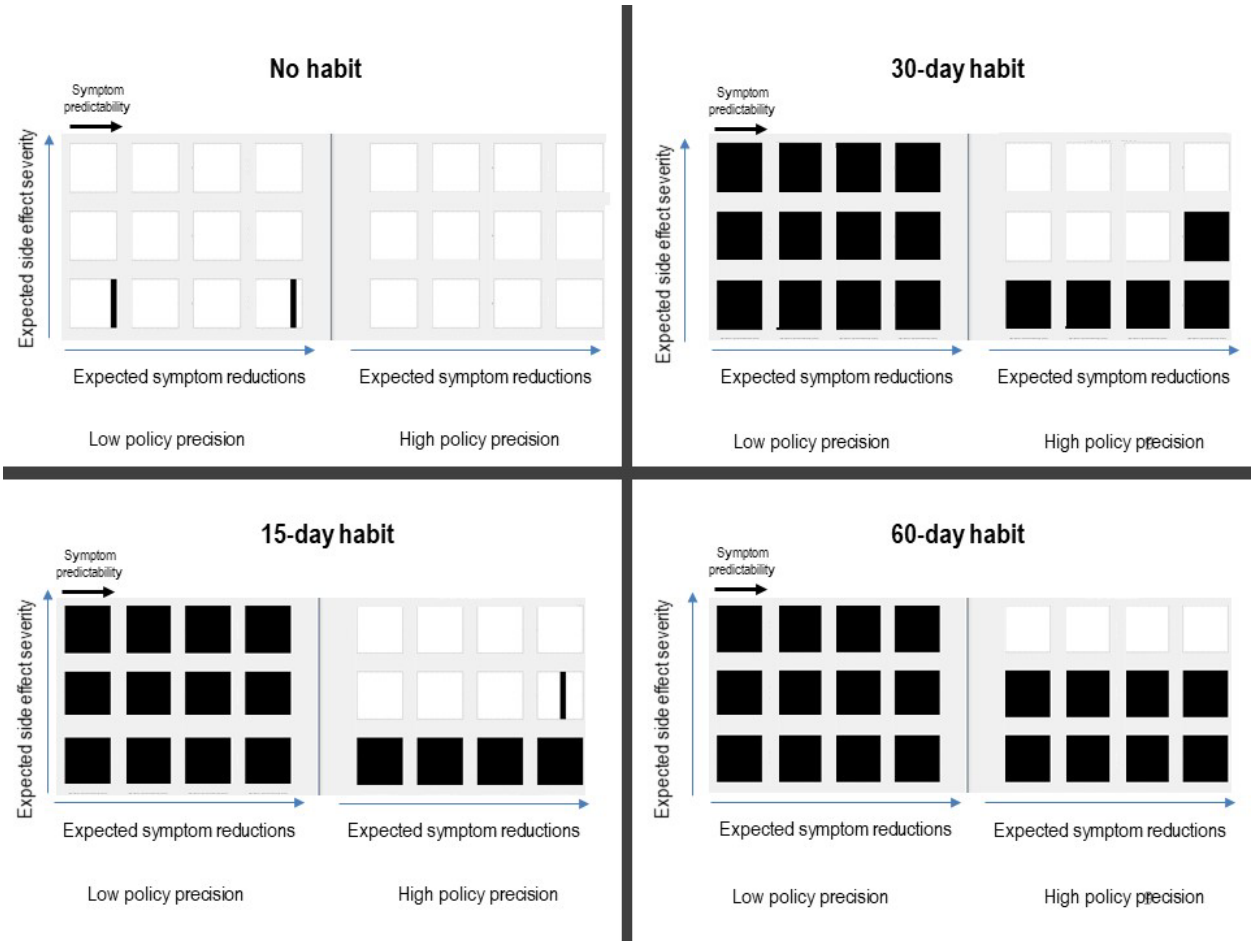


Figure 7. A depiction of the influence of habit formation at different habit strengths, based on the previous number of times (e.g., days) that an individual has chosen to take the medication previously, under different values for the other parameters in the model. Habit formation was modeled via manipulation of the **E**-matrix by increasing the probability, in terms of counts (i.e., 1, 15, 30, and 60 previous medication-taking decisions), of the medication-taking action relative to other allowable actions. Here the agent also had a policy depth of 1, such that she was not forward-looking beyond the immediate expected consequences of adhering. The agent otherwise had accurate expectations about the observations it would make under different actions. See main text for interpretation.

Discussion

We have used simulations to quantitatively demonstrate a number of distinct decision-making processes that could contribute to individual differences in adherence behavior. These simulations demonstrate the way in which an intuitively simple, binary (although clinically relevant) decision can be influenced by several underlying computational processes. This supports the plausibility of highly heterogeneous causes of non-adherence within and across populations of patients (for a summary of the different ways that adherence can break down, see column 4 of table 2). For example, while some patients may simply focus on proximal as opposed to distal future outcomes (i.e., low policy depth), others may focus on distal future outcomes but simply believe that those outcomes are either highly unreliable or that they will be worse overall if they follow treatment recommendations. Some patients may also be more plausibly characterized by intermediate combinations, such as intermediate policy depth and competing beliefs about moderately beneficial medication effects and moderately aversive side effects, both weighted by the relative confidence they have in each of those beliefs. Finally, differences in previous experience taking medication can lead to differences in adherence-promoting habit formation – where each of the other factors described above can influence how quickly such habits gain sufficient strength to maintain long-term adherence behavior. One advantage of the model we have presented is that each of these factors and their interactions can be simulated quantitatively at the level of an individual patient, where interesting "tipping points" can be identified where adherence begins to be favored over non-adherence in an individual's decision process.

At least three important research implications follow. First, it will be an important task to either identify or design simple measures (e.g., that could be administered in a clinic) capable of characterizing where an individual patient falls within the parameter space we have described. Such measures could potentially improve advanced prediction of who will and will not adhere. With respect to existing measures, the values for some parameters might be assessed by those used within the "necessity versus concerns" framework, such as the Beliefs about Medicines Questionnaire (12) or the revised Medication Adherence Reasons Scale (51) – perhaps most plausibly the parameters associated with beliefs about the magnitude of symptom reductions and side effects. In table 3, we have also listed a number of example self-report items that, based on the model we have described (and straightforward extensions of it), could be useful for gathering information about a patient's adherence-relevant beliefs. Once in a validated form, this type of questionnaire could be tested for its utility in predicting adherence behavior in advance.

The values of other parameters, in contrast, might be informed by personality measures. For example, the behavior associated with the personality variables of persistence (20) and locus of control (26) could follow from a combination of beliefs in high future predictability and high policy precision (and likely preferences with strong magnitudes as well). Low self-efficacy (21) could instead follow from a combination of low policy precision and precise expectations for non-preferred outcomes (while optimism may correspond to precise expectations for preferred outcomes, perhaps with or without taking medication – which could explain why more optimistic individuals are less likely to adhere; (24)). This is speculative, however, and will need to be examined in future work.

A second implication is that it will be important within the field of computational psychiatry to attempt to develop tasks, or find ways of acquiring detailed adherence behavior

data, that could be used in conjunction with a formal model (such as the one we described above) to explicitly fit to patient behavior. This would potentially allow for a more detailed and informative way to phenotype decision-making processes within individual patients. It should be mentioned, however, that this may be challenging due to the fact that the behavior in question involves simple binary decisions. That is, if multiple parameter value combinations can produce the exact same behavior, this prevents identification of unique parameter values that best explain individual patients' behavior. As such, this endeavor will likely require use of very detailed behavioral data, perhaps involving day by day medication-taking actions.

A third implication pertains to the need for effective adherence-promoting interventions. As reviewed above, current interventions have met with limited success (36), and we speculate this could be due to heterogeneity in underlying mechanisms as well as a failure to specifically target those mechanisms. Based on the factors highlighted in our model, we believe it might be possible to improve the ability of current interventions (or design new interventions) to intervene in a targeted manner. The degree of modifiability in those factors, such as individuals' policy depths, implicit beliefs about symptom predictability, and so forth is an open question, but certainly one worth pursuing. Based on our simulations, we would predict that each of the following should improve adherence:

1. Increasing future-oriented thinking (policy depth)
2. Attenuating overconfidence (prior policy precision)
3. Ensuring accurate expectations about symptom and side effect trajectories

It is important to stress the oversimplified and incomplete nature of the model we have presented. When presenting simulation results, one must unavoidably make somewhat arbitrary decisions about the values that should be assigned to fixed parameters (and what parameters to

fix). For example, we chose to set the preference magnitudes for side effects and symptom levels to specific values, and the simulation results would be expected to differ somewhat if different values had been chosen. In principle, simulations could also have been run at different values for this parameter, which would have led to an even higher dimensional space than we have presented. We also did not manipulate beliefs about the predictability of side effects, which could also plausibly influence adherence decisions. In these cases, we instead chose to hold these factors fixed and examine the effect of altering the dynamics of observed symptoms/side effect levels over time on versus off treatment.

There may also be additional factors that were not modeled explicitly, but that could be simulated within the model we have presented (and in principle be used in characterizing patients' decisions). For example, some individuals may simply forget to take their medication a couple of times and then cease altogether (51). In our model, this could be captured in part by low policy precision (i.e., increasing randomness in behavior), but would need to be combined with other factors such as the belief that all progress has been lost (as could be encoded within the individual's transition beliefs [**B**-matrix]). As another example, some people might cease medication after experiencing symptom improvement because they expect such improvements to remain stable after ceasing to take the drug (and the belief that side effects would go away). This could also be captured in our model with straightforward adjustments to the **B**-matrix.

Such limitations aside, we believe our model represents an important first step in gaining a more detailed understanding of the underlying factors and dynamics that influence a patient's decision to follow medical treatment recommendations. Because of the model's generality, it can also be very easily extended to model adherence to other medications, simply by inserting the symptom reduction and side effect profiles that characterize those medications. For example, it

follows from the general model structure that adherence to immediately rewarding medications (e.g. benzodiazepines) would be high and promote fast habit information, but behavior would also be influenced by the same parameters used here to investigate antidepressant adherence. The next steps in using these models will require identifying means of empirically characterizing and intervening on these mechanisms in an individualized manner.

Software note

Although the generative model – specified by the various matrices described in this paper – changes from application to application, the belief updates are generic and can be implemented using standard routines (here **spm_MDP_VB_X.m**). These routines are available as Matlab code in the SPM academic software: http://www.fil.ion.ucl.ac.uk/spm/. The simulations in this paper can be reproduced via running the Matlab code included here as supplementary material (**adherence_model.m**).

Acknowledgments

The authors have no funding sources or other acknowledgments to report.

Financial Disclosure

All authors reported no biomedical financial interests or potential conflicts of interest.

References

1. Aikens JE, Klinkman MS (2012): Changes in patients' beliefs about their antidepressant during the acute phase of depression treatment. *General hospital psychiatry*. 34:221-226.
2. Bosworth HB, Granger BB, Mendys P, Brindis R, Burkholder R, Czajkowski SM, et al. (2011): Medication adherence: a call for action. *American heart journal*. 162:412-424.
3. Serna MC, Cruz I, Real J, Gasco E, Galvan L (2010): Duration and adherence of antidepressant treatment (2003 to 2007) based on prescription database. *European psychiatry : the journal of the Association of European Psychiatrists*. 25:206-213.
4. Olfson M, Marcus SC, Tedeschi M, Wan GJ (2006): Continuity of antidepressant treatment for adults with depression in the United States. *The American journal of psychiatry*. 163:101-108.
5. Kim KH, Lee SM, Paik JW, Kim NS (2011): The effects of continuous antidepressant treatment during the first 6 months on relapse or recurrence of depression. *Journal of affective disorders*. 132:121-129.
6. Yue Z, Cai C, Ai-Fang Y, Feng-Min T, Li C, Bin W (2014): The effect of placebo adherence on reducing cardiovascular mortality: a meta-analysis. *Clinical research in cardiology : official journal of the German Cardiac Society*. 103:229-235.
7. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. (2006): A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ (Clinical research ed)*. 333:15.
8. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A (2008): Adherence to Mediterranean diet and health status: meta-analysis. *BMJ (Clinical research ed)*. 337:a1344.
9. Gibbons RD, Hur K, Bhaumik DK, Mann JJ (2005): The relationship between antidepressant medication use and rate of suicide. *Archives of general psychiatry*. 62:165-172.
10. Beatty L, Binnion C (2016): A Systematic Review of Predictors of, and Reasons for, Adherence to Online Psychological Interventions. *International journal of behavioral medicine*. 23:776-794.
11. Murata A, Kanbayashi T, Shimizu T, Miura M (2012): Risk factors for drug nonadherence in antidepressant-treated patients and implications of pharmacist adherence instructions for adherence improvement. *Patient preference and adherence*. 6:863-869.
12. Horne R, Weinman J, Hankins M (1999): The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology & Health*. 14:1-24.
13. De las Cuevas C, Penate W, Sanz EJ (2014): Risk factors for non-adherence to antidepressant treatment in patients with mood disorders. *European journal of clinical pharmacology*. 70:89-98.
14. Burnett-Zeigler I, Kim HM, Chiang C, Kavanagh J, Zivin K, Rockefeller K, et al. (2014): The association between race and gender, treatment attitudes, and antidepressant treatment adherence. *International journal of geriatric psychiatry*. 29:169-177.
15. Stetler C (2014): Adherence, expectations and the placebo response: why is good adherence to an inert treatment beneficial? *Psychol Health*. 29:127-140.

16. van Geffen EC, Heerdink ER, Hugtenburg JG, Siero FW, Egberts AC, van Hulten R (2010): Patients' perceptions and illness severity at start of antidepressant treatment in general practice. *The International journal of pharmacy practice*. 18:217-225.
17. Phillips LA, Diefenbach MA, Kronish IM, Negron RM, Horowitz CR (2014): The necessity-concerns framework: a multidimensional theory benefits from multidimensional analysis. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine*. 48:7-16.
18. Foot H, La Caze A, Gujral G, Cottrell N (2016): The necessity-concerns framework predicts adherence to medication in multiple illness conditions: A meta-analysis. *Patient education and counseling*. 99:706-717.
19. Cloninger CR, Przybeck TR, Svrakic DM (1991): The Tridimensional Personality Questionnaire: U.S. normative data. *PsycholRep*. 69:1047-1057.
20. Cloninger CR, Zohar AH, Hirschmann S, Dahan D (2012): The psychological costs and benefits of being highly persistent: personality profiles distinguish mood disorders from anxiety disorders. *Journal of affective disorders*. 136:758-766.
21. Judge TA, Erez A, Bono JE, Thoresen CJ (2002): Are measures of self-esteem, neuroticism, locus of control, and generalized self-efficacy indicators of a common core construct? *Journal of personality and social psychology*. 83:693-710.
22. Burra TA, Chen E, McIntyre RS, Grace SL, Blackmore ER, Stewart DE (2007): Predictors of self-reported antidepressant adherence. *Behavioral medicine (Washington, DC)*. 32:127-134.
23. Vangeli E, Bakhshi S, Baker A, Fisher A, Bucknor D, Mrowietz U, et al. (2015): A Systematic Review of Factors Associated with Non-Adherence to Treatment for Immune-Mediated Inflammatory Diseases. *Advances in therapy*. 32:983-1028.
24. Kronstrom K, Karlsson H, Nabi H, Oksanen T, Salo P, Sjosten N, et al. (2014): Optimism and pessimism as predictors of initiating and ending an antidepressant medication treatment. *Nordic journal of psychiatry*. 68:1-7.
25. Duckworth AL, Kern ML (2011): A Meta-Analysis of the Convergent Validity of Self-Control Measures. *Journal of research in personality*. 45:259-268.
26. Voils CI, Steffens DC, Flint EP, Bosworth HB (2005): Social support and locus of control as predictors of adherence to antidepressant medication in an elderly population. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 13:157-165.
27. Hong TB, Oddone EZ, Dudley TK, Bosworth HB (2006): Medication barriers and anti-hypertensive medication adherence: the moderating role of locus of control. *Psychology, health & medicine*. 11:20-28.
28. Gardner B, de Bruijn GJ, Lally P (2011): A systematic review and meta-analysis of applications of the Self-Report Habit Index to nutrition and physical activity behaviours. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine*. 42:174-187.
29. Bolman C, Arwert TG, Vollink T (2011): Adherence to prophylactic asthma medication: habit strength and cognitions. *Heart & lung : the journal of critical care*. 40:63-75.
30. Kothe EJ, Sainsbury K, Smith L, Mullan BA (2015): Explaining the intention-behaviour gap in gluten-free diet adherence: The moderating roles of habit and perceived behavioural control. *Journal of health psychology*. 20:580-591.

31. Lally P, van Jaarsveld CHM, Potts HWW, Wardle J (2010): How are habits formed: Modelling habit formation in the real world. *European Journal of Social Psychology*. 40:998-1009.
32. Vergouwen AC, Bakker A, Katon WJ, Verheij TJ, Koerselman F (2003): Improving adherence to antidepressants: a systematic review of interventions. *The Journal of clinical psychiatry*. 64:1415-1420.
33. Akerblad AC, Bengtsson F, Ekselius L, von Knorring L (2003): Effects of an educational compliance enhancement programme and therapeutic drug monitoring on treatment adherence in depressed patients managed by general practitioners. *International clinical psychopharmacology*. 18:347-354.
34. Peveler R, George C, Kinmonth AL, Campbell M, Thompson C (1999): Effect of antidepressant drug counselling and information leaflets on adherence to drug treatment in primary care: randomised controlled trial. *BMJ (Clinical research ed)*. 319:612-615.
35. Brook OH, van Hout H, Stalman W, Nieuwenhuyse H, Bakker B, Heerdink E, et al. (2005): A pharmacy-based coaching program to improve adherence to antidepressant treatment among primary care patients. *Psychiatric services (Washington, DC)*. 56:487-489.
36. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. (2014): Interventions for enhancing medication adherence. *The Cochrane database of systematic reviews*.CD000011.
37. Friston K, Stephan K, Montague R, Dolan R (2014): Computational psychiatry: the brain as a phantastic organ. *The lancet Psychiatry*. 1:148-158.
38. Huys Q, Maia T, Frank M (2016): Computational psychiatry as a bridge from neuroscience to clinical applications. *Nature Neuroscience*. 19:404-413.
39. Montague P, Dolan R, Friston K, Dayan P (2012): Computational psychiatry. *Trends in Cognitive Sciences*. 16:72-80.
40. Petzschner F, Weber L, Gard T, Stephan K (2017): Computational Psychosomatics and Computational Psychiatry: Toward a Joint Framework for Differential Diagnosis. *Biological Psychiatry*. 82:421-430.
41. Friston K, FitzGerald T, Rigoli F, Schwartenbeck P, Pezzulo G (2017): Active Inference: A Process Theory. *Neural Computation*. 29:1-49.
42. Hieronymus F, Nilsson S, Eriksson E (2016): A mega-analysis of fixed-dose trials reveals dose-dependency and a rapid onset of action for the antidepressant effect of three selective serotonin reuptake inhibitors. *Transl Psychiatry*. 6:e834.
43. Crawford AA, Lewis S, Nutt D, Peters TJ, Cowen P, O'Donovan MC, et al. (2014): Adverse effects from antidepressant treatment: randomised controlled trial of 601 depressed individuals. *Psychopharmacology (Berl)*. 231:2921-2931.
44. Doshi F, Pineau J, Roy N (2008): Reinforcement Learning with Limited Reinforcement: Using Bayes Risk for Active Learning in POMDPs. *Proc Int Conf Mach Learn*. 301:256-263.
45. Kaelbling LP, Littman ML, Cassandra AR (1998): Planning and acting in partially observable stochastic domains. *Artificial Intelligence*. 101:99-134.
46. Friston K, Parr T, de Vries B (2017): The graphical brain: Belief propagation and active inference. *Network Neuroscience*. 1:381-414.
47. Friston K, Rosch R, Parr T, Price C, Bowman H (2018): Deep temporal models and active inference. *Neuroscience & Biobehavioral Reviews*. 90:486-501.

48. Parr T, Friston K (2018): The Discrete and Continuous Brain: From Decisions to Movement—and Back Again. *Neural Computation*.1-29.
49. Parr T, Markovic D, Kiebel S, Friston K (2019): Neuronal message passing using Mean-field, Bethe, and Marginal approximations. *Scientific Reports*. 9:1889.
50. Friston K, Lin M, Frith C, Pezzulo G, Hobson J, Ondobaka S (2017): Active Inference, Curiosity and Insight. *Neural Computation*. 29:2633-2683.
51. Unni EJ, Olson JL, Farris KB (2014): Revision and validation of Medication Adherence Reasons Scale (MAR-Scale). *Current medical research and opinion*. 30:211-221.

Table 1. Model variables

Model variable	General Definition	Model-specific specification
o_t	Observable outcomes at time t	Outcome modalities: 1. Depressive symptoms severity (0 - 10) at each week of treatment. 2. Side effect severity (0 - 3) at each week of treatment.
s_t	Hidden states at time t	Hidden state factors: 1. Perceived quality of life (0 - 12) at each week of treatment. 2. Adherence vs. non-adherence at each week of treatment.
π	A distribution over action policies encoding the predicted value of each policy.	Allowable policies included the decision to continue taking the medication over 12 weeks or to cease medication at any week prior to week 12.
A matrix $p(o_t \mid s_t)$	A matrix encoding beliefs about the relationship between hidden states and observable outcomes (i.e., the probability that specific outcomes will be observed given specific hidden states).	Encodes beliefs about the relationship between perceived quality of life, adherence decisions, depressive symptoms, and side effects.
B matrix $p(s_{t+1} \mid s_t)$	A matrix encoding beliefs about how hidden states will evolve over time (transition probabilities).	Encodes beliefs about the way quality of life will change given the choice to adhere or not adhere at each week of treatment.
C matrix $p(o_t)$	A matrix encoding the degree to which some observed outcomes are preferred over others (technically modeled as prior expectations over outcomes).	Encodes the stronger preference for lower depressive symptoms and lower side effect severities.
D matrix $p(s_1)$	A matrix encoding beliefs about (a probability distribution over) initial hidden states.	The simulated agent always begins in an initial state of being "undecided" about choosing to adhere or not, and always begins in an initial state of being at the lowest perceived quality of life.

E matrix $p(\pi)$	A matrix encoding beliefs about what actions will be chosen a priori (a prior probability distribution over policies), based on the number of times different actions of been chosen in the past.	Higher values in this matrix indicate a greater number of previous choices to adhere vs. not adhere to medications in the past.

Table 2. Model parameters

Parameter	Formal definition	Brief explanation	Observed effects
Objective symptom predictability	The standard deviation of a Gaussian probability density function specified over the **A** matrix in the generative process that produces observed symptom reductions over time when choosing to take the medication.	Lower levels of predictability (a high standard deviation) indicate that changes in symptoms while on medication will be less stable/predictable (around the mean trajectory) from week to week.	Generally, less predictable symptoms (greater day-to-day symptom fluctuations) deter adherence. Greater random (upward) fluctuations can also be sufficient in certain cases to change an individual's beliefs such that they now think the drug is ineffective.
Subjective symptom predictability	The standard deviation of a Gaussian probability density function specified over the **A** matrix encoding beliefs in the generative model about the symptom reductions that will be observed over time when choosing to take the medication.	Lower levels of predictability (a high standard deviation) indicate the prior belief that changes in symptoms while on medication will be less stable/predictable (around the mean trajectory) from week to week.	Overly optimistic beliefs about symptom predictability tend to promote adherence even in the face of highly fluctuating symptoms.
Objective medication response magnitude	A parameter that transforms (shifts) the **A** matrix in the generative process that produces observed symptom reductions over time when choosing to take the medication. This was specified as single symptom level shifts up and to the right from baseline mean symptom level trajectories (strong, moderate, weak, and very weak response magnitudes corresponded to 0, 1, 2, and 3 up/right shifts, respectively).	Lower response magnitude values indicate that there will be a longer delay before symptoms begin to decrease and that a smaller overall decrease in symptoms will be achieved by the final week of treatment.	Higher response magnitude promotes adherence because they more easily outweigh the individual's concerns about the side effects of the drug.
Subjective medication response magnitude	A parameter that transforms (shifts) the **A** matrix encoding beliefs in the generative model	Lower response magnitude values indicate the prior belief that there will	Overly optimistic beliefs about symptom response magnitudes show a trend toward improving adherence in some cases (but the

	about the symptom reductions that will be observed over time when choosing to take the medication. This was specified as single symptom level shifts up and to the right from baseline mean symptom level trajectories (strong, moderate, weak, and very weak response magnitudes corresponded to 0, 1, 2, and 3 up/right shifts, respectively).	be a longer delay before symptoms begin to decrease and that a smaller overall decrease in symptoms will be achieved by the final week of treatment.	effects are complex).
Objective side effect severity	A parameter that transforms (shifts) the **A** matrix in the generative process that produces observed side effects over time when choosing to take the medication. This was specified as shifts upward or downward one level in the baseline side effect time course (severe, moderate, and mild levels corresponded to shifts of 1, 0, and -1, respectively).	Lower side effect severity indicates that milder side effects will be experienced initially, and that they will eventually become less over time.	Higher side effect severity promotes non-adherence in general, as more severe side effects are not preferred.
Subjective side effect severity	A parameter that transforms (shifts) the **A** matrix encoding beliefs in the generative model about the side effects that will be observed over time when choosing to take the medication. This was specified as shifts upward or downward one level in the baseline side effect time course (severe, moderate, and mild levels corresponded to shifts of 1, 0, and -1, respectively).	Lower side effect severity indicates the prior belief that milder side effects will be experienced initially, and that they will eventually become less over time.	Overly optimistic beliefs about side effects promote non-adherence, because they lead to immediate disappointment upon observing higher-than-expected side effect levels.
Policy depth	The number of time steps over which action policies are specified. This ranged from 1 to 12 weeks,	Lower policy depth indicates that, when people are deciding whether or not to	A high policy depth promotes adherence when an individual expects that, despite initially feeling worse (or not improving), in the long

	indicating the distance in the future one considers when planning how to act. A 12-week time period was chosen to match with the typical timeframe studied in antidepressant drug trials.	adhere, they do not consider the changes in symptoms and side effects that will occur as far into the future. For example, they might think "I'm not going to take the medication because it's going to make me feel bad tomorrow" without considering that it will make them feel much better after several weeks.	run they will ultimately feel better overall.
Prior policy precision (**β**)	An "inverse temperature" parameter modulating the impact of current beliefs on policy selection. Encodes how confident an individual is in general in their ability to make the best decision regarding adherence. High precision was modeled with a value of 1, and low precision was modeled with a value of 10.	Lower policy precision (higher **β** values) indicates less confidence in the choice to adhere vs. not adhere in general.	Lower policy precision tends to promote adherence in the context of pessimistic beliefs about the overall effectiveness of medication. For example, an individual who does not believe the medication is likely to help may still "give the medication a try" if they have less confidence that their beliefs will lead to the best decision.
Habit strength	Magnitude of the prior expectation in the **E** matrix that the decision to adhere will be chosen – based on the number of times the individual has chosen to take the medication in the past.	Higher medication-taking habit strength reduces the influence of explicit beliefs about the consequences of taking medication on decision-making.	Higher medication-taking habit strength promotes adherence, even if an individual doesn't have strong beliefs that the medication will increase their quality of life overall. Adherence is chosen "out of habit" without consideration of expected effects.

Table 3: Assessment questions motivated by our model:

We would like to ask you about your beliefs regarding different experiences you may have when you take medications or engage in other types of treatment for your mental health condition.

Sometimes how people feel (and other symptoms) can change a lot from day-to-day. How much do you think your symptoms will change from one day to the next if you were to take the medication? (1 = not at all, 10 = quite a lot)

Not at all **Quite a lot**

1 2 3 4 5 6 7 8 9 10

How much do you think your symptoms will change from one day to the next if you choose not to take the medication? (1 = not at all, 10 = quite a lot)

Not at all **Quite a lot**

1 2 3 4 5 6 7 8 9 10

If you take the medication regularly starting today, how do you think you will feel in two weeks? (1 = about the same as now, 10 = my symptoms will go away completely)

About the same as now **Completely well (no symptoms)**

1 2 3 4 5 6 7 8 9 10

If you take the medication regularly starting today, how do you think you will feel after several months? (1 = about the same as now, 10 = my symptoms will go away completely)

About the same as now **Completely well (no symptoms)**

1 2 3 4 5 6 7 8 9 10

If you do not start treatment now, how do you think you will feel in two weeks? (1 = about the same as now, 10 = my symptoms will go away completely)

About the same as now **Completely well (no symptoms)**

1 2 3 4 5 6 7 8 9 10

If you do not start treatment now, how do you think you will feel after several months? (1 = about the same as now, 10 = my symptoms will go away completely)

About the same as now **Completely well (no symptoms)**

1 2 3 4 5 6 7 8 9 10

How much does how you feel (and other symptoms) interfere with your usual activities? (1 = does not interfere at all, 10 = interferes with all activities)

Does not interfere at all **Interferes with all activities**

1 2 3 4 5 6 7 8 9 10

If you take the medication regularly starting today, how certain are you that you will experience unwanted effects from the treatment? (1 = highly uncertain, 10 = highly certain)

Highly Uncertain **Highly Certain**

1 2 3 4 5 6 7 8 9 10

If you take the medication regularly starting today, how much do you think unwanted effects from the treatment will interfere with your usual activities in the first two months? (1 = will not interfere at all, 10 = will interfere with all activities)

Will not interfere at all **Will interfere with all activities**

1 2 3 4 5 6 7 8 9 10

How do you think unwanted effects from the treatment will change in the long-term? (Circle one)

They will get worse **They will stay the same** **They will eventually get better**

How much do you think unwanted effects of treatment will change from day to day if you choose to take the medication? (1 = at all, 10 = quite a lot)

Not at all **Quite a lot**

1 2 3 4 5 6 7 8 9 10

If the treatment makes you feel better, what do you think will happen if you stop taking the medication? (Circle one)

I will feel worse again **I will continue to feel better**

How certain are you that this belief is accurate? (1 = highly uncertain, 10 = highly certain)

Highly Uncertain **Highly Certain**

1 2 3 4 5 6 7 8 9 10

Sometimes people are surprised by how much better or worse they feel when they take medications. How likely do you think it is that the medication will make you feel better than you expect? (1 = very unlikely, 10 = very likely)

Very Unlikely **Very Likely**

1 2 3 4 5 6 7 8 9 10

How likely do you think it is that the medication will make you feel worse than you expect? (1 = very unlikely, 10 = very likely)

Very Unlikely **Very Likely**

1 2 3 4 5 6 7 8 9 10

People do not always get everything done that they set out to do on a daily basis. For example, sometimes people forget about a task that they intended to complete. How often does this happen to you? (1 = never, 10 = all the time)

Never **All the Time**

1 2 3 4 5 6 7 8 9 10

Have you taken any psychiatric medications in the past? (Circle one)

No Yes

If so:

How long did you take them? (Circle one)

less than 2 weeks **2 – 4 weeks** **1 – 3 months** **3 – 6 months** **greater than 6 months**

And how often did you accidentally forget to take them on average? (Circle one)

never **less than 1 time per month** **1 time per month** **2 times per month**

1 time per week **greater than 1 time per week**

Have you generally had a negative or positive experience when taking medications previously? (1 = extremely negative, 10 = extremely positive)

Extremely Negative **Extremely Positive**

1 2 3 4 5 6 7 8 9 10