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On the behavioral economics of medication choice: A research story

David P. Jarmolowicz[a,b,*], Derek D. Reed[a,b], Amanda S. Bruce[c,d], Jared M. Bruce[e,f]

[a] University of Kansas, Department of Applied Behavior Science, United States
[b] University of Kansas, Cofrin Logan Center for Addiction Research and Treatment, United States
[c] University of Kansas Medical Center, Department of Pediatrics, United States
[d] Children's Mercy Hospital, Center for Children's Healthy Lifestyles, United States
[e] University of Missouri – Kansas City, Department of Psychology, United States
[f] University of Missouri – Kansas City. Department of Biological and Health Informatics, United States

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ABSTRACT

Behavioral economics has been consistently useful in describing a wide range of clinical phenomena, particularly in reference to behavioral excesses such as substance abuse, problematic gambling and obesity/overeating. Given an opportunity to explore these processes as they relate to treatment adherence in patients with multiple sclerosis (MS), our central thesis was that behavioral economic tools/processes that have been helpful in other areas of application (e.g., substance abuse, obesity) could be leveraged to help understand treatment non-adherence and hopefully lead to efforts to combat it. The current paper tells a story of how an interdisciplinary set of researchers came to combine their separate expertise in MS and behavioral economics to yield novel insights into the failures of treatment adherence often experienced in this clinical population.

1. Introduction

There are several approaches to writing a mini-review. For example, reviews written in large research areas can follow one of the well-established protocols such as the Cochrane system. This approach is fair, unbiased, and provides a workable summary as a starting point as a research area moves forward. Alternatively, researchers can provide a selective review that helps build a case for a particular theoretical point (e.g., Bickel et al., 2012b, 2000; Green and Myerson, 2013; Rachlin, 2006; Shahan and Craig, 2017). These reviews risk bias, yet they bring research areas together and the theoretical insight that they provide can often suggest research directions beyond the holes in the literature highlighted by systematic reviews. The current review, however, operates from a less common third tradition – inspired by Sidman's autobiographical description of early stimulus equivalence research (Sidman, 1994). This tradition, which emphasizes narrative storytelling (Hineline, 2018) without any veneer of objectiveness, has been gaining acceptance across a wide range of scientific disciplines (See the recent special issues in the *Psychological Record* and *Perspectives on Behavior Science* and the call for papers through *PLOS-One*). This highly personal approach may be appropriate given the relative paucity of research on the behavioral economics of treatment adherence (Stevens, 2014). This paper, written from the perspective of the first author with consultation from the remaining authors, summarizes a fruitful research line – adding to the previously published reports by providing context surrounding the experiments, models, and their evolution. The impetus for this research line was and continues to be applied in nature – specifically, to develop behavioral economic tools that help us understand and ultimately act upon medication non-adherence in patients with multiple sclerosis (MS). Given that this research was disseminated to a range of audiences, this work has the secondary purpose of bringing this work together in one place. No attempts are made to correct the errors of the research line's youth. Instead, our mistakes – and what we learned from them - are on display, highlighting that science is progressive and is the behavior of scientists (Skinner, 1957). Here is our story.[1]

As a new faculty member at the University of Kansas, I (David Jarmolowicz) had the privilege of giving a talk for the University of Missouri- Kansas City's Department of Psychology, where the Drs. Bruce (Amanda & Jared) were faculty. This talk was an overview of the behavioral economic research in the well-worn areas of substance abuse (Bickel et al., 2012c; Madden and Bickel, 2009; MacKillop et al., 2011), gambling (Dixon et al., 2003; Petry, 2001), and obesity (Jarmolowicz et al., 2014; Bickel et al., 2014; Rasmussen et al., 2010; Weller et al.,

* Corresponding author. 1000 Sunnyside Ave., Lawrence, KS, 66045, United States.
E-mail address: DPJ@KU.edu (D.P. Jarmolowicz).

[1] The portrait of the process reported here is through the rose-colored lens that we often view most successful collaborations. At each step in this process, there were intense debates, sometimes resulting in furious diagrams written on bar napkins. Interdisciplinary research is challenging, and we would not have it any other way.

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2008) – some of which Dr Reed (Derek) and I were conducting with Amanda (Jarmolowicz et al., 2014). The talk was well received, we celebrated with a lovely lunch, and went on our way.

A few weeks later, Amanda invited Derek and me to lunch to discuss the analysis of some behavioral economic data that she had collected examining rates of delay discounting in adults with obesity (Jarmolowicz et al., 2014). Jared joined the group. The tacos were delicious, the conversation was interesting, and we ended the meal with a plan for data analysis.

As the meal wound down, Jared asked a consequential question: "Do you know anything about MS?". The answer, of course, was "no". Jared, however, knew a lot about MS (Bruce et al., 2010a, 2010b; Bruce and Lynch, 2011) and described the complications he was facing as he tried to help MS patients take their medications. Specifically, many effective disease modifying treatments (DMTs; i.e., medications) were available to individuals suffering from MS (Guarnera et al., 2017; Milo, 2015), yet these patients often failed to take their DMTs as prescribed (Margolis et al., 2011; Bruce et al., 2016a, 2016b; Reynolds et al., 2010; Wong et al., 2011). Jared explained that when patients took their DMTs, they ran a risk of immediate and sometimes debilitating side effects, yet they felt no tangible symptom improvement. Instead, the medications worked by preventing the future worsening of their condition. Hence, the DMTs simply decreased the probability of their disease worsening yet bore a probability of immediate side effects. This seemed like a novel behavioral economics question, the answer to which could improve patients lives. Needless to say, we were interested in answering questions of that sort.

2. The first experiment

The result of this lunchtime discussion? An intellectual challenge. Jared was conducting a randomized controlled trial using telephone counseling to improve adherence among MS patients who chose not to take their DMTs against their doctor's advice (Bruce et al., 2016b). He wanted to develop a measure that incorporated patients' responses to the likelihood of patients experiencing DMT side effects as well as their probabilistic efficacy. This measure needed to be concise enough to administer quickly in the clinic, yet comprehensive enough to provide substantial information on effects of both decreasing efficacy and increasing likelihoods of side effects. Given the probabilistic nature of the treatment gains, the logical starting point was probability discounting (Rachlin et al., 1991), which describes how the value of an alternative systematically descreases as the liklihood of receiving it decreases. As we thought through issues of DMT adherence, we decided that patients likelihood of taking a medication was a workable proxy for their valuation of that DMT. As such, we adapted a progression of probabilities (i.e., 0.95, .90, .75, .50, .33, .10, .5) similar to those used in prior studies (Jones and Rachlin, 2009; Rachlin et al., 1991; Yi et al., 2007; Yi and Landes, 2012) to examine likelihood of efficacy across three probabilities of side effects (i.e., 0.10, 0.50, 0.90). By asking patients to report their likelihood of taking medications via a visual analog scale (Kaplan et al., 2014), this yielded a decision-making questionnaire with a total of 21 questions (see Appendix) that could easily be administered in the clinical setting.[2]

As a part of ongoing studies, Jared administered the task to 39 patients that were typically adherent (collected as part of a student's thesis project) with their DMTs and 38 that were not (collected as part of a treatment trial). As can be seen in Fig. 1, when the probabilities of efficacy (p) were converted to odds against efficacy ($\theta = \frac{1-p}{p}$) the patterns of responding were consistent with those obtained during more conventional probability discounting assessments (Rachlin et al., 1991; Green and Myerson, 2004; McKerchar et al., 2010; Yi et al., 2007, 2008). Moreover, the decrease in likelihood of taking medications as the odds against efficacy increased was more pronounced in patients that were non-adherent, relative to those that typically took their medicine as prescribed. Attempts were made to describe the data using Rachlin et al. (1991) modification of Mazur's hyperbolic formula (Mazur, 1987),

$$V = \frac{A}{1 + h\theta}, \tag{1}$$

where in the subjective value (V) of a given amount (A; assumed to be 100% with perfect efficacy and no side effect) of a commodity is discounted at a given rate (h) as the odds against treatment benefit (θ_e). Of note, the hyperbolic nature of this model assumes that value will decline sharply with initial decreases in efficacy and less so as efficacy continues to decline. Hence, the model assumes an oversized impact of small decrements in efficacy. The fits with this model, however, were moderate to very poor (r^2 = -1.91 – 0.86). This was disappointing. We found, however, that Myerson and Green's (1995) hyperboloid modification

$$V = \frac{A}{(1 + h\theta)^s}, \tag{2}$$

of Mazur's equation, which added a scaling parameter (s), better described the data (r^2 = 0.89 -0.99). This suggested that not only can these sorts of choices be well described by behavioral economic models, psychophysical scaling/weighting (Myerson et al., 2011) of probabilities may be an important component of these models.

Given that we were modeling these health behaviors in a clinical sample that we wished to help, a major component of our experimental focus was on assessing the relation between these patterns of decision making and clinical variables. As such, the plan was to incorporate findings from this analysis into regression models that predict important behavior such as DMT adherence status (i.e., were the patients typically adherent with DMT suggestions?). Our need to include the hyperboloid's scaling parameter in order to adequately model the data, however, preempted the use of discounting rate (i.e., h) as a predictor in our regression models. Specifically, given that h was not the only free parameter, it was not the sole representative of the curve. As such, we calculated area under the curve (AUC; Myerson et al., 2001),

$$AUC = \sum (x^n - x^{n-1})\left[\frac{y^{n-1} + y^n}{2}\right], \tag{3}$$

Using the trapezoid method which provided a single metric suitable to parametric statistics (i.e., regression). In examining AUC values via a 2 (group) x 3 (side effect probability) repeated measures ANOVA, we found a significant group (adherent vs nonadherent) by side effect probability (0.1, 0.5, 0.9) interaction ($F[1.74, 130.52] = 36.05$, $p < 0.001$) as well as significant main effects of side effect probability ($F[1.74, 130.52] = 9.84$, $p < 0.001$).

Most importantly, these AUC values and other MS relevant demographic variables (i.e., level of disability, depression symptoms, fatigue, gender, age, ethnicity, marital status, educational level, and disease duration) where used to build a logistic regression model aimed at classifying subjects as typically adherent or non-adherent. The purpose of this analysis was to determine if there were factors that were predictors of patients DMT adherence. Of these variables, the only significant predictor (β = -10.5, $p = 0.007$) was AUC for medications with infrequent side effects (i.e., .10 probability). These findings suggested that our newly established measure may be able to differentiate patients likely to take their DMTs as directed from those who would not. This may be important because identifying behavioral processes that predict

[2] Although AUC is often used as a measure of discounting, it is not a measure of discounting, per se. Instead, rather than quantifying how steep the regression line is, AUC quantifies how much space is below the curve. As such, the same AUC can be arrived at in several ways which differ in their relation to discounting rate. By contrast to discounting rate, however, AUC is particularly driven by differences at the high odds against/delays, whereas non-linear regression evenly weights data across all parameters.

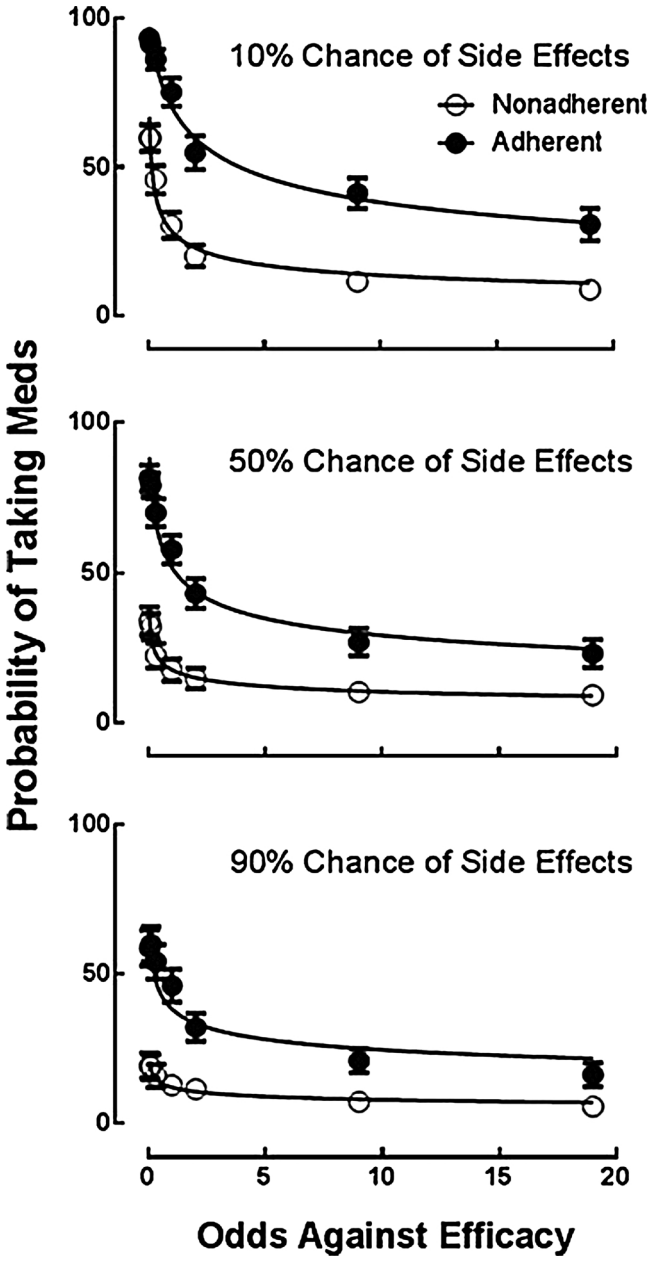


Fig. 1. Probability of taking medication (y-axis) at each odds against ratio (x-axis) in participants that were adherent (closed circles) or nonadherent (open circles) with medications when there was a 10% (top graph), 50% (middle graph), or 90% (bottom graph) chance of side effects, Solid lines represent hyperboloid model fits. Error bars show SEM. From Bruce et al., 2016a, 2016b.

whom is most likely to have difficulties with medication adherence allows clinicians to 1) direct assistance with medication adherence to those whom most need the help and/or 2) provide a behavioral process to target in efforts to improve adherence.

3. Learning more about these data

Findings of the initial study were quite reinforcing, and despite dispute of the mechanism driving it (Killeen and Jacobs, 2017; Shahan, 2017), reinforcement tends to lead to more of the reinforced behavior. As such, we revisited this initial dataset, looking to find additional order in the data. With offices sharing a wall and a tendency towards caffeine-fueled data discussions, Derek and I dug in - looking at the data in a myriad of sometimes interesting ways. From an applied standpoint, an important question became: Is there any way to take patients that normally fail to take their medications and make them more like those that typically take their medications? We, of course, had a lot of data to deal with to get there. The eventual solution was somewhat simple. Given the difficulties with AUC_2 (Borges et al., 2016), we built from prior work which had demonstrated that the point along a delay discounting curve at which value drops to 50% of its initial value is simply the inverse of k (i.e., delay discounting rate (k) as calculated via Mazur's (1987) formula [$V = A/1 + kD$] which describes how the value [V] of a given amount [A] of a commodity decreases as a function of the delay to receiving the commodity [D] – modulated by k).

$$ED50 = \frac{1}{k} \tag{4}$$

Specifically, we first calculated h, using Eq. (1). Next, consistent with Yoon and Higgins (2008), we calculated Eθ50 by taking the inverse of h.

$$E\theta 50 = \frac{1}{h} \tag{5}$$

This gave us the odds against at which the value of the probabilistic reward dropped by 50% of the undiscounted amount. Odds against, however, is not easily interpreted. Thus, we further converted the Eθ50 to EP50, using the following formula.

$$EP50 = \frac{1}{E\theta 50 + 1} \tag{6}$$

This provided a readily interpretable measure of the probability of efficacy at which patients were 50% likely to take their medications that we could calculate at each probability of side effects (Fig. 2). Unsurprisingly, a repeated measures ANOVA of these EP50 values found main effects of group ($F[1,75] = 526.47$, $p < .0001$) and side effect probability ($F[2,150] = 57.59$, $p < .0001$) as well as a significant interaction between the two ($F[1,150] = 4.48$, $p = 0.013$). Next, we fit linear functions to each individuals' EP50 data, allowing us to interpolate EP50 values at each potential probability of side effects (0–100%; 0.0005% intervals). Using these interpolated data, we used t-tests to compare the EP50 data at the typically adherent individuals' 100% chance to the typically non-adherent individuals' EP50 values at each possible chance of side effects. There was a small range of probability of side effects for typically non-adherent individuals wherein there were no significant differences in this analysis (Shaded). Thus, there was a range of side effect probabilities wherein typically non-adherent individuals would respond like typically adherent individuals (responding under poor conditions) – it was just not particularly large. Next, we repeated the process, comparing non-adherent patients' EP50 values when there was a 0% chance of side effects to every value calculated for the typically adherent patients. There was an area of overlap (shaded), the area was just not particularly large. Thus, although there were side effect ranges wherein, we could compel non-adherent patients to take medications, the relatively small range of values suggests that this may not be an easy feat. Hence, efforts to develop well-tolerated medications have a very small range of side effect probabilities to target.

Next, in addition to collecting the data described above, for one of Jared's students' thesis project, they collected additional data substituting the probability of side effects for severity of side effects (i.e., mild, moderate, vs. severe; (Jarmolowicz et al., 2017)). Forty-two typically DMT adherent MS patients were recruited from a large MS clinic run by our collaborator, Dr. Sharon Lynch (a neurologist whom is an accomplished MS researcher and clinician). These patients completed a 21-item questionnaire almost identical to the one used in the prior experiments (Appendix) with one exception. Instead of the probability of side effects being specified in each question, the severity of those side effects was specified. The results are shown in Fig. 3. In our initial analysis of the data, we found that Eq. (2) described the data well, with

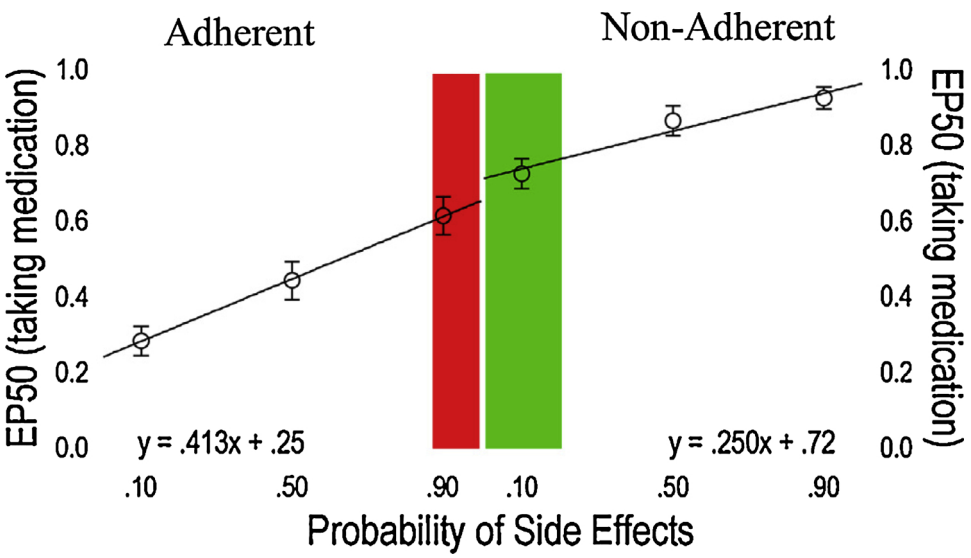


Fig. 2. Shows the mean indifference points (i.e., the probability of success at which their likelihood of taking medications drops to 50%; Effective Probability 50% [EP50])for individuals' decisions to take medications in the adherent group (left graph) and non-adherent group (right graph). The red shaded area shows the probabilities of adherent individuals side effects wherein t-tests on the forecasted data found that adherent individuals' choices did significantly ($p < 0.05$) differ from the choices that non-adherent individuals are forecasted to make under ideal circumstances (i.e., when the probability of side effects was 0%). The green shaded area shows the prob-abilities of side effects wherein nonadherent individuals' choices did not statistically differ ($p > 0.05$) from adherent individuals' choices under the most unfavorable conditions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) From Jarmolowicz et al., 2016.

a systematic increase in k as the side effects became more severe. An astute peer reviewer, however, helped me reconsider the analysis. Specifically, the reviewer pointed out that although the likelihoods of taking DMTs were lower with more severe side effects, the best fit lines seem to be parallel. Thus, the severity seemed to impact patients' overall likelihood of taking medications, not the slope associated with decreases in efficacy. This could be better reflected in allowing the undiscounted amount (A) to vary. As such, we re-analyzed the data using Eq. (1), but with A (i.e., Amount, in this case likelihood of taking perfectly effective medications that had no side effects) as a free parameter. This approach provided an excellent description of the individuals' choices involving mild (median $R^2 = 0.91$), moderate (median $R^2 = 0.92$), and severe (median $R^2 = 0.94$) side effects. Moreover, this analysis discriminated the main effect of side effect severity on overall likelihood of taking medications (reflected in A) from a difference in discounting (reflected in h).

4. Scaling up

As may be evident, Jared was a MS researcher with something of an understanding of the data needed to better facilitate DMT adherence in this population (Heesen et al., 2014). Fortunately, he felt that a better understanding of these decision-making processes was necessary and undertook the non-trivial task of securing funding to conduct additional research. As such, we secured the support of National Multiple Sclerosis Society to do a larger scale and more nuanced evaluation of these decision-making processes. With the goal being to develop a decision-making model that could guide both efforts to improve DMT adherence and drug development.

Over the next several months, Jared and his research group did the hard work. First, Jared and Amanda put together an extensive testing battery – consulting Derek and me on the behavioral economic components of the assessment. Next, with the help of their community partners (e.g., Dr. Lynch), they recruited over 300 patients with MS and administered an extensive testing battery to each patient (See Appendix B, for details). Finally, Jared and his group organized this immense pile of data into a form that could be logically interpreted. A subset of which he sent to Derek and me for analyses.

As a follow-up to our prior work on effects of DMT efficacy and probability of side effects, the centerpiece to this project was a comprehensive analysis of interactive influence of side effect severity, side effect probability, and % efficacy of DMTs. Specifically, MS patients completed the comprehensive testing battery which included a probability discounting task wherein patients reported their likelihood of taking a medication across a range of side effect probabilities (11 values, ranging from 0.1% to 99.9%) side effect severities (mild, moderate, and severe) and medication efficacies (11 values, ranging from 0.1% to 99.9%). This resulted in a lot of data – which is the best sort of problem to have.

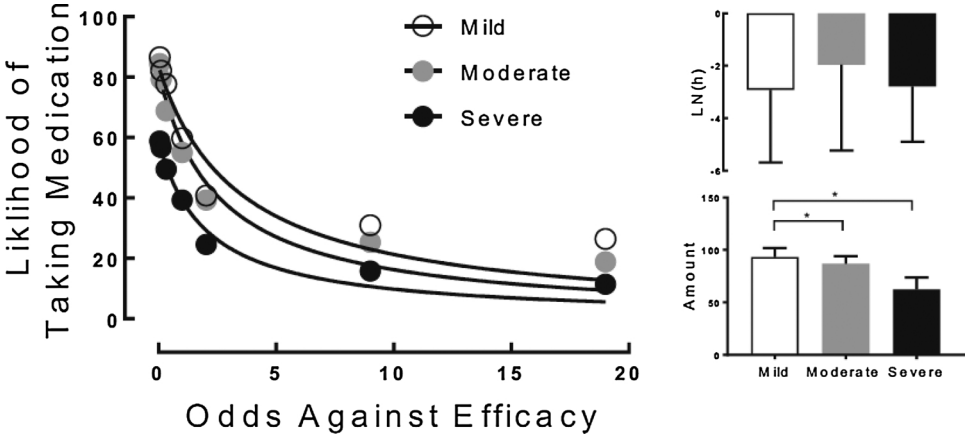


Fig. 3. Left graph shows the probabilities of taking medications (y-axis) at each odds against treatment success (x-axis) on questions with mild (open circles), moderate (gray circles), or severe (closed circles). The top right graph shows delay discounting rates (LN[k]) for each side effect severity (different color bars), with error bars showing the 95% confidence interval. The bottom right graph shows the value of A (i.e., fitted parameter showing likelihood of taking medications when they are 100% effective) for each side effect severity (different color bars), with error bars showing the 95% confidence interval. Asterisk indicates statistically significant ($p = 0.001$) comparisons. From Jarmolowicz et al., 2017.

Probability of Side Effects

Medication Efficacy

MILD	0.1%	1.0%	5.0%	15.0%	34.0%	50.0%	66.0%	85.0%	95.0%	99.0%	99.9%
0.1%	7.62	5.83	5.38	4.66	4.00	3.76	3.66	3.55	3.69	3.34	3.38
1.0%	10.34	8.59	6.83	6.1	5.03	4.90	4.72	4.62	4.34	4.00	4.07
5.0%	22.45	16.52	12.66	9.72	8.34	8.21	7.34	7.07	7.14	6.59	6.28
15.0%	33.79	28.1	23.66	18.86	14.00	13.72	12.41	11.45	10.86	10.55	10.34
34.0%	49.76	44.14	39.31	33.97	26.55	23.76	21.90	19.90	18.83	18.10	17.72
50.0%	64.97	63.24	58.48	52.24	43.79	38.00	34.76	31.07	29.55	29.86	28.83
66.0%	75.45	73.45	69.72	63.66	53.93	48.79	43.59	38.48	36.62	36.66	36.21
85.0%	89.24	88.59	85.76	79.48	68.69	62.00	57.79	51.52	48.59	47.83	46.45
95.0%	94.17	94.69	91.97	86.83	77.45	69.66	66.69	59.28	55.17	53.93	53.21
99.0%	95.52	96.17	93.76	89.21	79.90	71.48	68.38	61.17	56.72	55.45	54.69
99.9%	95.72	95.90	93.97	89.28	80.38	71.79	68.59	61.55	57.24	55.79	55.03
MODERATE	0.1%	1.0%	5.0%	15.0%	34.0%	50.0%	66.0%	85.0%	95.0%	99.0%	99.9%
0.1%	8.34	6.52	4.93	3.90	3.21	2.86	2.79	2.55	2.28	1.76	2.31
1.0%	10.38	7.90	5.69	4.97	4.21	3.86	3.38	3.14	2.79	2.28	2.21
5.0%	16.34	12.62	10.07	7.72	6.59	5.90	5.69	5.21	4.83	4.31	4.14
15.0%	26.93	21.34	17.69	13.55	11.52	10.28	9.38	8.62	7.45	6.90	6.62
34.0%	42.34	38.48	33.83	29.07	22.10	19.34	18.00	15.31	14.03	13.34	13.00
50.0%	60.38	54.79	50.79	45.48	38.21	32.66	29.59	25.48	23.00	22.48	21.79
66.0%	70.62	67.00	62.17	56.83	48.86	43.03	38.76	32.69	29.62	28.90	27.97
85.0%	84.79	82.83	79.24	74.72	64.38	58.28	52.86	45.34	40.90	39.17	38.52
95.0%	90.24	30.03	87.28	83.62	73.66	66.14	61.24	54.24	48.86	46.17	44.66
99.0%	91.76	91.41	89.03	84.13	74.97	68.24	62.90	56.07	51.59	48.52	46.34
99.9%	91.83	91.62	89.21	85.17	75.24	68.52	63.21	56.48	52.03	48.83	46.72
SEVERE	0.1%	1.0%	5.0%	15.0%	34.0%	50.0%	66.0%	85.0%	95.0%	99.0%	99.9%
0.1%	4.62	2.86	2.00	1.90	1.66	1.62	1.48	0.79	0.93	0.52	0.52
1.0%	5.45	3.21	2.69	2.38	2.14	1.76	1.55	0.83	0.97	0.52	0.52
5.0%	8.79	5.17	3.83	3.72	3.10	2.38	1.93	1.24	1.34	0.90	0.69
15.0%	16.00	11.31	8.59	6.55	5.38	4.24	3.38	2.38	1.97	1.48	1.21
34.0%	27.34	22.41	18.41	15.31	11.76	9.28	7.72	4.45	3.93	2.97	2.66
50.0%	40.48	35.48	31.76	27.86	21.79	17.45	14.21	8.93	7.59	5.72	5.55
66.0%	49.10	45.07	41.21	36.90	29.79	24.10	19.62	12.34	10.59	8.31	7.69
85.0%	62.48	59.97	54.83	49.45	41.10	34.21	28.52	18.62	16.14	12.90	11.55
95.0%	70.21	68.93	63.45	58.17	48.93	41.14	35.21	26.17	20.45	16.17	14.31
99.0%	72.24	71.38	66.34	60.62	51.31	43.17	36.59	28.41	22.10	17.79	16.03
99.9%	72.66	71.69	67.24	60.79	51.90	43.48	36.93	29.00	22.59	18.45	16.45

Fig. 4. Mean likelihood that participants would initiate a disease-modifying therapy at each efficacy and probability of side effects. Red indicates below 50% likelihood, yellow indicates not significantly different from 50% likelihood (decision switch points), and green indicates above 50% likelihood. For example, if there was a 5% chance of severe side effects and a 85% reduction in disease activity (efficacy), patients on average reported a 55% likelihood they would take the DMT. From Bruce et al., 2018a, 2018b.

4.1. Describing the data

Our first pass at reporting these data was descriptive (Bruce et al., 2018b). Jared had an approach to reporting the data that gave a straight forward picture of what we had seen (Fig. 4). Specifically, Jared presented patients' mean likelihood taking their DMT at each X (probability of side effect) Y (medication efficacy) coordinate for DMTs with mild (top panel), moderate (center panel), or severe side effect (bottom panel) – with shading of the boxes providing additional cues to the choice patterns. The data were systematic, highlighting the interaction amongst these three powerful variables. Clearly, patients' propensity to take medications was an orderly function of these three variables. A repeated measures ANOVA with Greenhouse-Geisser correction found an overall effect of side effect severity ($F[1.42, 409.39] = 321.89$, $p < 0.001$) on patients' willingness to take their DMTs. Looking at the data in a different way (Fig. 5), the percentage of patients that reported a > 50% chance of taking DMTs at each X (probability of side effect) Y (medication efficacy) coordinate was similarly impacted by these same interactive variables, providing some potential guidance for drug development and testing.

4.2. Modeling the data

The next step was to build from our prior work to model these data (Jarmolowicz et al., 2018a). Despite our group having experience in quantitative analysis, this was a challenging process. These were four-dimensional (probability of taking medications x side effect severity x side effect probability x percent efficacy) data unlike any that we had previously encountered. We were, however, not completely out on a limb. Vanderveldt et al. (2015) had done some excellent work wherein they developed a three-dimensional model to examine effects of rewards being both probabilistic and delayed. Specifically, they found that a multiplicative model,

$$V = \frac{A}{[(1 + kD)^{s_d*}(1 + h\theta)^{s_p}]}, \quad (7)$$

wherein A, k, h, θ, and s were as defined above, provided a much better description of the data than an additive model (also see, Cox and Dallery, 2016). These findings suggest that not only did delay and probability interact to alter reinforcer value, the interaction was multiplicative in nature. Taking Vanderveldt et al. as a starting point, we set

Probability of Side Effects

Medication Efficacy

MILD	0.1%	1.0%	5.0%	15.0%	34.0%	50.0%	66.0%	85.0%	95.0%	99.0%	99.9%
0.1%	7.62	5.83	5.38	4.66	4.00	3.76	3.66	3.55	3.69	3.34	3.38
1.0%	10.34	8.59	6.83	6.1	5.03	4.90	4.72	4.62	4.34	4.00	4.07
5.0%	22.45	16.52	12.66	9.72	8.34	8.21	7.34	7.07	7.14	6.59	6.28
15.0%	33.79	28.1	23.66	18.86	14.00	13.72	12.41	11.45	10.86	10.55	10.34
34.0%	49.76	44.14	39.31	33.97	26.55	23.76	21.90	19.90	18.83	18.10	17.72
50.0%	64.97	63.24	58.48	52.24	43.79	38.00	34.76	31.07	29.55	29.86	28.83
66.0%	75.45	73.45	69.72	63.66	53.93	48.79	43.59	38.48	36.62	36.66	36.21
85.0%	89.24	88.59	85.76	79.48	68.69	62.00	57.79	51.52	48.59	47.83	46.45
95.0%	94.17	94.69	91.97	86.83	77.45	69.66	66.69	59.28	55.17	53.93	53.21
99.0%	95.52	96.17	93.76	89.21	79.90	71.48	68.38	61.17	56.72	55.45	54.69
99.9%	95.72	95.90	93.97	89.28	80.38	71.79	68.59	61.55	57.24	55.79	55.03
MODERATE	0.1%	1.0%	5.0%	15.0%	34.0%	50.0%	66.0%	85.0%	95.0%	99.0%	99.9%
0.1%	8.34	6.52	4.93	3.90	3.21	2.86	2.79	2.55	2.28	1.76	2.31
1.0%	10.38	7.90	5.69	4.97	4.21	3.86	3.38	3.14	2.79	2.28	2.21
5.0%	16.34	12.62	10.07	7.72	6.59	5.90	5.69	5.21	4.83	4.31	4.14
15.0%	26.93	21.34	17.69	13.55	11.52	10.28	9.38	8.62	7.45	6.90	6.62
34.0%	42.34	38.48	33.83	29.07	22.10	19.34	18.00	15.31	14.03	13.34	13.00
50.0%	60.38	54.79	50.79	45.48	38.21	32.66	29.59	25.48	23.00	22.48	21.79
66.0%	70.62	67.00	62.17	56.83	48.86	43.03	38.76	32.69	29.62	28.90	27.97
85.0%	84.79	82.83	79.24	74.72	64.38	58.28	52.86	45.34	40.90	39.17	38.52
95.0%	90.24	30.03	87.28	83.62	73.66	66.14	61.24	54.24	48.86	46.17	44.66
99.0%	91.76	91.41	89.03	84.13	74.97	68.24	62.90	56.07	51.59	48.52	46.34
99.9%	91.83	91.62	89.21	85.17	75.24	68.52	63.21	56.48	52.03	48.83	46.72
SEVERE	0.1%	1.0%	5.0%	15.0%	34.0%	50.0%	66.0%	85.0%	95.0%	99.0%	99.9%
0.1%	4.62	2.86	2.00	1.90	1.66	1.62	1.48	0.79	0.93	0.52	0.52
1.0%	5.45	3.21	2.69	2.38	2.14	1.76	1.55	0.83	0.97	0.52	0.52
5.0%	8.79	5.17	3.83	3.72	3.10	2.38	1.93	1.24	1.34	0.90	0.69
15.0%	16.00	11.31	8.59	6.55	5.38	4.24	3.38	2.38	1.97	1.48	1.21
34.0%	27.34	22.41	18.41	15.31	11.76	9.28	7.72	4.45	3.93	2.97	2.66
50.0%	40.48	35.48	31.76	27.86	21.79	17.45	14.21	8.93	7.59	5.72	5.55
66.0%	49.10	45.07	41.21	36.90	29.79	24.10	19.62	12.34	10.59	8.31	7.69
85.0%	62.48	59.97	54.83	49.45	41.10	34.21	28.52	18.62	16.14	12.90	11.55
95.0%	70.21	68.93	63.45	58.17	48.93	41.14	35.21	26.17	20.45	16.17	14.31
99.0%	72.24	71.38	66.34	60.62	51.31	43.17	36.59	28.41	22.10	17.79	16.03
99.9%	72.66	71.69	67.24	60.79	51.90	43.48	36.93	29.00	22.59	18.45	16.45

Fig. 5. Percentage of patients who reported greater than 50% likelihood that they would take a disease modifying therapy at each efficacy side effect combination. Deep red indicates _10%, light red indicates between 10% and 50%, light green indicates between 50% and 90%, and deep green indicates 90%. For example, if there was a 66% chance of moderate side effects and a 34% reduction in disease activity (efficacy), 8% of patients indicated that they would likely take the medication. From Bruce et al., 2018a, 2018b.

out to incorporate the lessons we had learned in our prior work into a comprehensive model that described likelihood of taking a DMT given the probability of side effects and percent efficacy. Specifically, the modeling will require a weighting/scaling parameter (Bruce et al., 2016a) to account for how patients weight side effects and efficacy and if we wanted to make comparisons across side effect severities and we needed to leave the undiscounted amount as a free parameter (Jarmolowicz et al., 2017). Moreover, Vanderveldt et al. had taken the very reasonable step of using differing scaling parameters for differing discounting rates (i.e., s_d vs s_p). Although both of our dimensions were probabilistic, we had no compelling reason to believe that efficacy and probability of side effects would be weighted similarly. Lastly, the likelihood of taking DMTs would likely decrease as the probability of side effects increased and decrease as the percent efficacy decreased. This would yield functions unlike those that we were accustomed to interpreting. As such, we converted percent efficacy into odds against efficacy as described above, but converted probability of side effects into the mathematically inverse odds of side effects ($\theta = p/(1-p)$). This yielded a model,

$$V = \frac{U}{[(1 + h_e\theta_e^{s_e})*(1 + h_{se}\theta_{se}^{s_{se}})]}, \quad (8)$$

which described how the value (V; i.e., likelihood of taking the DMT) of a DMT decreases as the odds against efficacy (θ_e) increase and the odds of side effects (θ_{se}) increase, with this relation being modulated by the patients undiscounted likelihood of taking the medication (U), the rate at which they discount based on decreasing efficacy (h_e) or increasing chances of side effects (h_{se}) and their weighting of that efficacy (s_e) and side effect probability (s_{se}). Uncomfortable with the model's five free parameters, we evaluated several leaner iterations of the model, each providing a lesser empirical and conceptual fit to the data (see Table 1). This full model, however, described the data well (see Fig. 6) as patients made decisions about medications with mild side effects (curves fit to means, $r^2 = 0.96$; curves fit to individual patients data, Median $r^2 = 0.93$, IQR = 0.87, 0.96), moderate side effects (curves fit to means, $r^2 = 0.97$; curves fit to individual patients data, Median $r^2 = 0.94$, IQR = 0.89, 0.97), and severe side effects (curves fit to means, $r^2 = 0.98$; curves fit to individual patients data, Median $r^2 = 0.94$, IQR = 0.90, 0.96). By modeling these data, we were able to precisely isolate the roles of patients' probability discounting/scaling based on side effects (i.e., h_{se} s_{se}) and decreases in efficacy (i.e., h_e s_e). These findings suggest that our behavioral economic models could be adapted to describe the complex decision-making processes that MS patients use as choosing to/not to take their DMTs (Fig. 7).

Moreover, the individual parameter values from each side effect severity empirically varied in expected ways. For example, consistent

Table 1
Fit of a variety of models to Jarmolowicz et al., 2018a, 2018b data. From Jarmolowicz et al., 2018a, 2018b.

			Model fitting parameters					
Model (V =)			r^2	U	h_e	h_{se}	s_e	s_{se}
$\frac{U}{(1+h_e\partial^{Se})*(1+h_{se}\partial^{Sse})}$	Means	Mild	0.96	100	0.68	0.29	0.89	0.22
		Moderate	0.97	100	0.84	0.38	0.96	0.24
		Severe	0.98	86.45	1.22	1.22	0.95	0.36
	Medians	Mild	0.95	100	1.08	0.20	0.23	1.33
		Moderate	0.96	100	1.20	0.31	0.32	1.47
		Severe	0.98	91.25	2.08	1.18	1.07	1.35
$\frac{U_{observed}}{(1+h_e\partial^{Se})*(1+h_{se}\partial^{Sse})}$	Means	Mild	0.76	94.38	0.52	0.36	0.20	$8.6*10^3$
		Moderate	0.32	91.38	0.89	0.33	$2.1*10^7$	0.77
		Severe	0.98	73.18	1.12	0.64	0.47	1.08
	Medians	Mild	0.95	100	1.08	0.20	0.23	1.33
		Moderate	0.96	100	1.20	0.31	0.32	1.47
		Severe	0.98	90	2.05	1.15	1.09	1.38
$\frac{U}{(1+h_e\partial)*(1+h_{se}\partial)}$	Means	Mild	0.85	77.32	0.69	0.001		
		Moderate	0.84	73.37	0.86	0.001		
		Severe	0.94	70.05	1.25	0.43		
	Medians	Mild	0.90	89.25	1.32	0.001		
		Moderate	0.88	94.55	1.38	0.04		
		Severe	0.98	95.70	1.99	1.19		
$\frac{U}{(1+h_e\partial^{S})*(1+h_{se}\partial^{S})}$	Means	Mild	0.89	100	1.05	0.08	0.44	
		Moderate	0.89	100	1.17	0.15	0.45	
		Severe	0.96	80.27	1.37	0.60	0.64	
	Medians	Mild	0.90	87.69	1.30	0.002	1.12	
		Moderate	0.89	105.83	1.48	0.13	0.67	
		Severe	0.98	90.95	2.04	1.13	1.22	

with Jarmolowicz et al. (2017) the undiscounted likelihood of taking the medications significantly differed across side effect severities ($H_{[2]} = 92.31$, $p < .0001$) with post hoc differences observed between discounting with mild versus severe ($p < .0001$) side effects and discounting with moderate versus severe ($p < 0.0001$) side effects. Similar severity based differences were seen for discounting based on side effects (H[2] = 50.28, $p < .0001$), scaling/weighting of side effects (H[2] = 66.50, $p < .0001$), and discounting based on efficacy (H[2] = 27.19, $p < 0.0001$), but not scaling/weighting of efficacy (H[2] = 5.09, $p = .08$). Given the strong empirical and theoretical fits of the model, and the responsiveness of the model to changes in side effect severity, we had reason to believe that this model may provide clinically meaningful data.

4.3. Using the data

These findings were exciting, but with each of us having applied roots (Derek and I in Applied Behavior Analysis, Jared and Amanda in clinical psychology), we were most interested in the applied implications of this work. In fact, one of the primary selling points of behavioral economics is its ability to describe – and often predict – clinically relevant phenomena (Jarmolowicz et al., 2016). Hence, the next step was to determine if data from our model similarly described important clinical phenomena. Fortunately, knowing that our interest would shift in this direction, Jared/Amanda included a number of clinical measures that are well validated for use with MS patients in our assessment battery (see Bruce et al., 2018a for summary).

As a result, the next step was to look for relations between our modeling parameters and these clinical measures (Bruce et al., 2018a). We, however, were working with a lot of data – increasing our chance of false positives. As a result, we restricted our analysis. Specifically, we only looked for relations in our patients with relapsing remitting multiple sclerosis (RRMS) (n = 208 [after exclusions]; 80% currently taking DMTs), the only MS subtype for which DMTs are approved for use. Moreover, based on our prior findings regarding the propensity of patients' likelihood of taking DMTs when there was a small chance of side effects, we restricted our analysis to the data we had on patients' likelihood of taking DMTs when there was a risk of mild side effects.

The results were encouraging. Consistent with our prior analysis, Eq. (8) provided an excellent description of the data (r^2 for aggregate data = 0.96; mean r^2 = 0.90; SD = 0.09). As noted above, although a majority of our patients were taking DMTs, some were not. A Kruskal-Wallis test found that patients who were currently taking DMTs discounted those medicines less robustly based on increasing side effect probability ($X^2 = 5.14$, p = 0.02) than those that were not, suggesting that probability discounting may play a direct role in MS patients DMT adherence. Because there was substantial skew and kurtosis in the distributions of our discounting parameters, we chose to compare patients in the middle of these distributions (i.e., second and third quartile) to those with the lowest (i.e., first quartile) and highest (i.e., fourth quartile) parameter values.

First, we examined relations between discounting based on side effects (h_{se}) and our clinical measures. When groups were formed based on h_{se} (i.e., top 25% h_{se}, middle 50% h_{se}, and bottom 25% h_{se}) the groups did not differ on age, education, sex, disability status or disease duration. An ANOVA, however, found significant group differences in patients knowledge about their disease ($F[2,205] = 12.76$; $p < 0.001$), with follow-up tests (Tukey HSD) showing that patients with low h_{se} had greater MS Knowledge that patients with moderate ($p = 0.04$) or high ($p < 0.001$) h_{se}. Additionally, Adherence Determination (i.e., intention to take their medications) differed between groups ($F[2,205] = 9.62$; $p < 0.001$), with follow-up analysis showing that patients with low h_{se} had greater Adherence Determination that patients with moderate ($p = 0.003$) or high ($p < 0.001$) h_{se}. Consistent with this finding, a Chi square found that Likelihood of non-adherence (missing 20% or more of doses) also differed between groups ($X^2 = 13.07$, $p = 0.001$) with follow-up X^2 revealing that patients with high h_{se} (27%, 11/41) were more likely than patients with moderate (10%, 8/80; $X^2 = 5.8$, $p = 0.02$) or low h_{se} (2%, 1/46; $X^2 = 11.08$, $p = 0.001$) to be non-adherent (Bruce et al., 2018a). Hence, patients rate of discounting based on side effects was related to patients' disease knowledge, adherence determination, and actual adherence –highlighting the clinical utility of our behavioral economic model.

Next, we assessed relations between discounting based on decreasing efficacy (h_e) and our clinical measures. As with groupings based on h_{se}, grouping based on h_e did not differ on education, sex, disability status or disease duration. The groups did, however, differ based on age – with low rate discounters being older than moderate rate

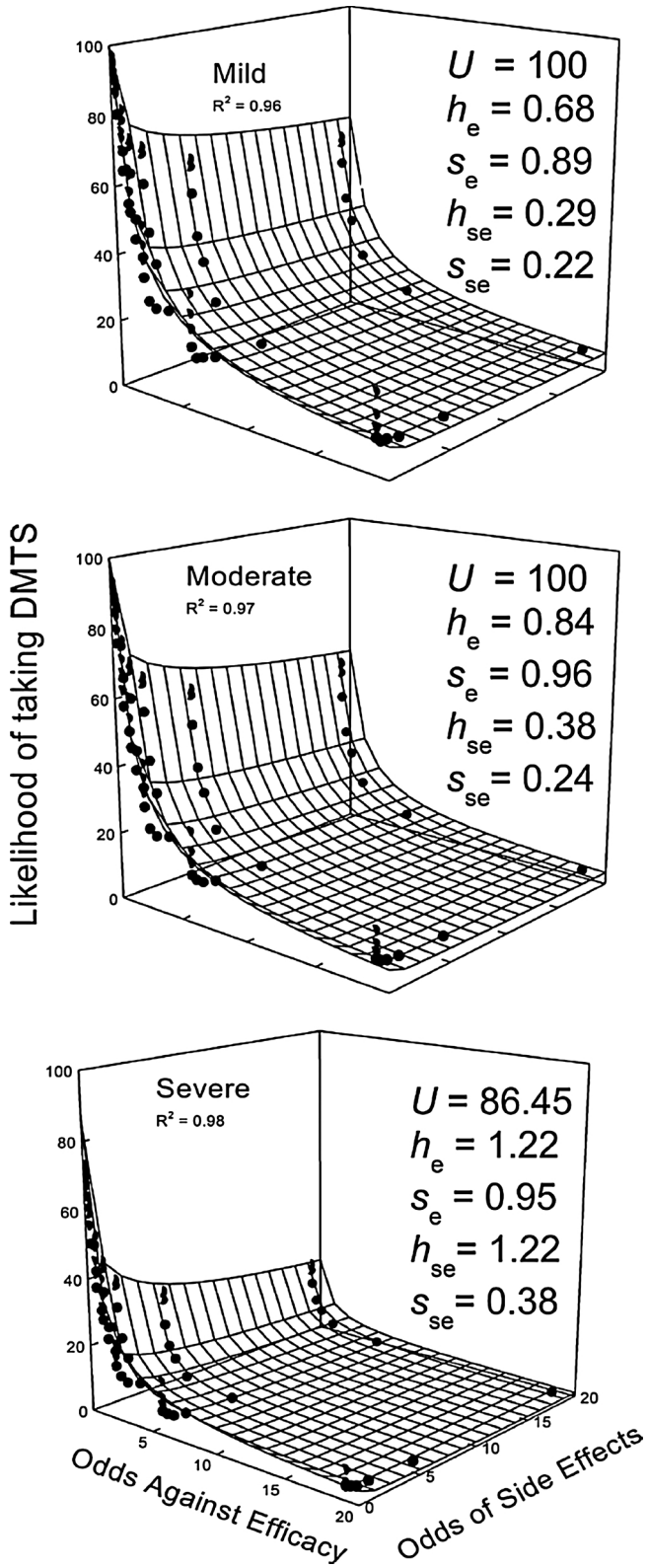


Fig. 6. Patients likelihood of taking DMTs at each efficacy and side-effect probability when the side effects were mild (top panel), moderate (middle panel), and severe (bottom panel). The undiscounted amount (*U*), discounting of efficacy (*he*) and side effects (*hse*) as well as scaling of side efficacy (*se*) and side effects (*sse*) from models run on these group average data are embedded in each figure. From Jarmolowicz et al., 2018a, 2018b.

discounters (cf. Green et al., 1994). An ANOVA with Welsh correction found that scores on our cognitive tests differed across these groups ($F[2,96.59) = 3.25$, $p = 0.04$), with follow-up Tamhane tests showing that patients with high h_e underperformed patients with moderate h_e ($p = 0.04$). Hence, patient cognitive state appears to be significantly related to discounting based on side effects, further highlighting the clinical utility of our model and the specificity of various model components (i.e., h_e related to cognition, but not adherence related variables).

Next, we examined relations between likelihood of taking optimal DMTs and our clinical measures. Because a majority (i.e., 82.2%) of patients reported that they would always take and optimal mediation ($U = 100$), we divided the patients into those with $U = 100$ and those with $U < 100$. Groups did not differ based on did not differ on age, education, sex, disability status or disease duration. Like h_e, groups based on U differed in their cognitive performance ($t[205] = 3.35$, $p = 0.001$), with patients with lower U values performing more poorly.

The final step was to develop a regression model which leveraged these findings to predict patient adherence. Because MS knowledge and h_{se} were both related to adherence group status (i.e., patients taking ≥ 80% of prescribed doses were classified as adherent), a logistic regression model was developed to determine which of these variables accounted for unique variance in adherence group status. Only h_{se} accounted for unique variance in adherence group membership ($X^2 = 12.95$, Nagelkerke $R^2 = 0.14$, $p < 0.001$). Hence, specific components (h_{se}) of our behavioral economic model, representing specific behavioral processes, were uniquely well-suited as predictors of medication adherence.

5. What we have learned

Keep in mind, we started this process with little if any understanding of how behavioral economics intersected with medication adherence. Derek and I entered this process with a vague thesis that because behavioral economics and behavioral economic tools have been useful in conceptualizing a range of other disorders (Bickel et al., 2012a, 2011; Jarmolowicz et al., 2016), that they may be helpful in this case. Jared and Amanda came to the table with a sense of the clinical phenomenon, a taste of behavioral economics, and an educated guess that they would fit together. Any success we have had in describing these behavioral patterns is a testament to leaps of faith – and tasty tacos.

In the end, the discounting toolbox that we have used to describe our relationship with so many other commodities/phenomena seem to have proven useful. Specific to probability discounting, the current data suggest that the same general mathematical relation that has been so successfully used to describe devaluation of commodities such as money (Jarmolowicz et al., 2012; Rachlin et al., 1991; Yi et al., 2007), sex (Lemley et al., 2018; Lawyer and Schoepflin, 2013; Johnson et al., 2015) can be used to describe how patients' choices interact with medication efficacy and the likelihood of side effects. This may help pave a path for additional behavioral economic extensions into health behavior (cf. Jarmolowicz et al., 2018b).

Importantly, we found that this modified probability discounting approach yielded data that were uniquely suited to understanding treatment adherence. Specifically, across multiple studies we have been able to develop significant predictors of treatment adherence (Bruce et al., 2016a,2016b, 2018a,2018b). From a clinical perspective, this may provide either predictors of treatment prognosis or targets to improve adherence.

Lastly, through this process, we have learned much more about quantitative modeling than expected. Consistent with Vanderveldt et al., a three-dimensional model provided an excellent description of

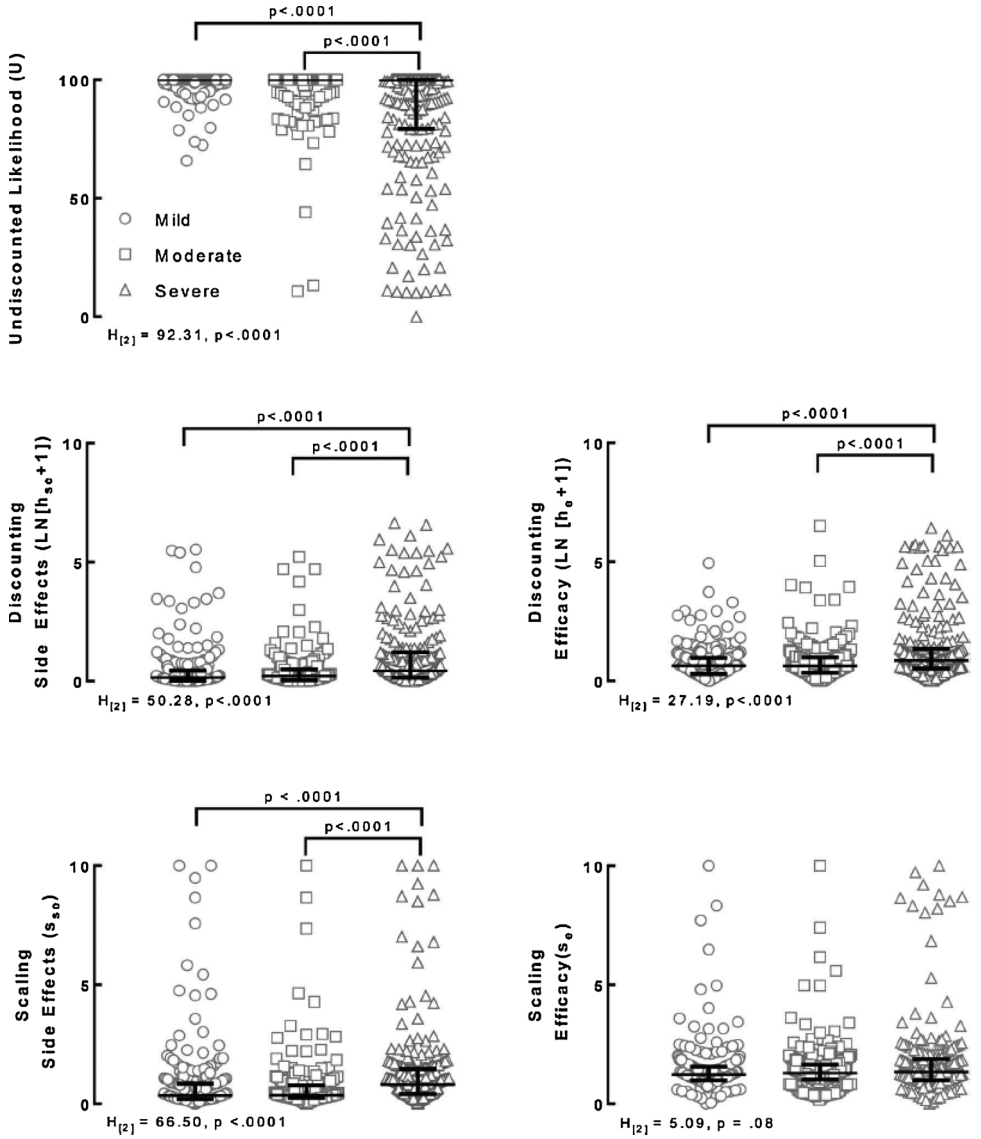


Fig. 7. Parameter estimates for models fit to each individuals' responses regarding mild (circles), moderate (boxes), and severe (triangles) side effects. Medians and IQR are shown by horizontal bars and error bars. From Jarmolowicz et al., 2018a, 2018b.

the data. We, however, extended from outcomes that were both probabilistic and delayed, to outcomes that incorporated two different probabilistic components. Despite both being probabilistic, however, differing discounting and scaling parameters were needed to account for the data. From a clinical perspective, this made sense. Patients' surely weight side effects and medication efficacy differently, even though both are probabilistic. Said another way, weighting/scaling of efficacy and side effects may show domain specificity (Lawyer and Schoepflin, 2013). Hence, variables that impact one specific domain may not impact other domains (e.g., administering cocaine impacts discounting of sex, but not discounting of money (Johnson et al., 2017)), despite both domains being representations of the same process. This possibility, and a greater understanding of the mechanisms driving these sorts of choices awaits additional research.

Harnessing the benefits and power of behavioral economics may have future implications for better treatment approaches, or more individualized treatment methods (precision medicine). More tacos may be required, and we look forward to it.

Appendix A. Questionnaire used in first experiment

Medical Decision Making Questionnaire

When thinking about whether to take or not to take a Disease Modifying Medication, patients must weigh the potential costs and benefits associated with each decision. Please indicate how likely you would be to take a Disease Modifying Medication if each of the following statements were true.

1. Taking Disease Modifying Medication has a **10%** chance of making you ill with side effects now, but also a **95%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

2. Taking Disease Modifying Medication has a **10%** chance of making you ill with side effects now, but also a **90%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

3. Taking Disease Modifying Medication has a **10%** chance of making you ill with side effects now, but also a **75%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

4. Taking Disease Modifying Medication has a **10%** chance of making you ill with side effects now, but also a **50%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

5. Taking Disease Modifying Medication has a **10%** chance of making you ill with side effects now, but also a **33%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

11. Taking Disease Modifying Medication has a **50%** chance of making you ill with side effects now, but also a **50%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

12. Taking Disease Modifying Medication has a **50%** chance of making you ill with side effects now, but also a **33%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

13. Taking Disease Modifying Medication has a **50%** chance of making you ill with side effects now, but also a **10%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

14. Taking Disease Modifying Medication has a **50%** chance of making you ill with side effects now, but also a **5%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

15. Taking Disease Modifying Medication has a **90%** chance of making you ill with side effects now, but also a **95%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

16. Taking Disease Modifying Medication has a **90%** chance of making you ill with side effects now, but also a **90%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

17. Taking Disease Modifying Medication has a **90%** chance of making you ill with side effects now, but also a **75%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

18. Taking Disease Modifying Medication has a **90%** chance of making you ill with side effects now, but also a **50%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

19. Taking Disease Modifying Medication has a **90%** chance of making you ill with side effects now, but also a **33%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

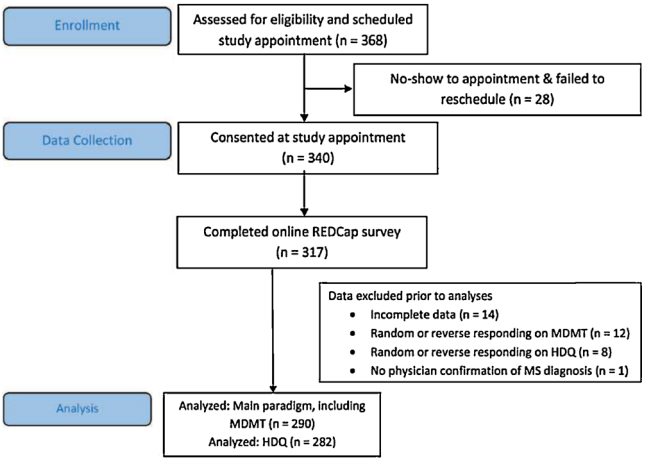
20. Taking Disease Modifying Medication has a **90%** chance of making you ill with side effects now, but also a **10%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

21. Taking Disease Modifying Medication has a **90%** chance of making you ill with side effects now, but also a **5%** chance of making you feel better over the next 5 years (i.e., due to fewer relapses, slower disease progression). Would you take this medication? (Place an "X" on the line indicating the likelihood of your taking this medicine)

will take	Might take	Will not take
100%	50%	0%

Appendix B. CONSORT diagram of study inclusion for data analyses. REDCap _ Research Electronic Data Capture; MDMT _ medical decision-making task; HDQ _ Health Decision Questionnaire. See the online article for the color version of this figure. From Bruce et al., 2018a, 2018b



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