The Potential Cost-Effectiveness of Psychedelic-Assisted Therapy for Initial Treatment of Major Depressive Disorder: A Decision Analytic Model

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Abstract

Major depressive disorder (MDD) is a leading cause of disability in the US and around the world, as well as a significant economic burden. The current standards of care include second-generation antidepressants (SGA) and cognitive behavioral therapy (CBT), but recent studies of psychedelic-assisted therapy (PAT) have shown promising results. This study replicates and validates a deterministic Markov model used previously to study the cost-effectiveness of SGA and CBT for patients with newly diagnosed MDD, then extends it to include PAT as a first-line alternative before patients move on to SGA or CBT. Under conservative parameter assumptions for PAT, the results suggest it would become cost-effective within 2-3 years, and robustly cost-saving after 5 years. While these results are favorable to PAT, much more clinical research, modeling, and legal work must occur before it can enter the standard mental healthcare paradigm.

1 | Introduction

Major depressive disorder (MDD) affects over 260 million people worldwide, including over 16.1 million adults in the US (6.7% of US adult population).[1] MDD is also the leading cause of disability and healthcare expenditures in the world. In the US, it is the leading cause of disability for adults ages 15-44 and costs the healthcare system over $200 billion annually.[2,3]

The American College of Physicians currently recommends that adults with MDD either receive treatment with a second-generation antidepressant (SGA) or cognitive behavioral therapy (CBT).[4,5] Meta-analyses have suggested that there are no statistically significant differences between SGA and CBT in initial efficacy, relapse rates, or discontinuation due to adverse events.[4] While a majority of patients with MDD reportedly prefer psychotherapy to

pharmacotherapy, survey data suggests that fewer than 25% receive psychotherapy.[6,7] A recent study comparing the cost-effectiveness of the two treatments for patients newly diagnosed with MDD found that CBT was cost-saving compared to SGA over a 5-year time horizon, however, it was not particularly cost-effective over a 1-year period (incremental cost-effectiveness ratio [ICER] from societal perspective = $186,000/QALY).[8]

In recent years there has been a growing interest in a new type of treatment for MDD as well as other mental illnesses: psychedelic-assisted therapy (PAT). PAT sessions involve the "ingestion of a psychedelic substance in a safe setting, supervised by trained therapists, and are often combined with preparatory and integratory sessions."[9] Michael Pollan's 2018 book, *How to Change Your Mind*, is recommended for an extensive history of the use, research, and legality of psychedelic substances.[10] This paper will focus on studies conducted since 2016 on the use of psilocybin (the active ingredient in magic mushrooms) for treating patients with some form of depression.

In 2016, two studies evaluated the effects of PAT on cancer patients with end-of-life anxiety and depression. Both used randomized, double-blind, cross-over trial designs with 29 and 51 patients, and saw similar effect sizes on depression rating scales (Cohen's D = 1.32 over 6 weeks and 1.3 over 5 weeks, respectively).[11,12] Between 2016 and 2018, researchers at Imperial College London began studying PAT on patients with treatment-resistant depression. They used a randomized, open-label design with no control, but observed a large average effect size from baseline after five weeks (Cohen's D = 2.3).[13,14] The same researchers later conducted a double-blind, randomized controlled trial comparing PAT and escitalopram (an SGA) on patients with long-standing MDD. The PAT group showed larger average effect sizes over six weeks, but the difference was not quite statistically significant under an alpha level of 0.05.[15] The most recent and perhaps most relevant study, published in 2022, included a 12-month follow-up on 24 patients with MDD. The randomized, waiting-list controlled study

found an average effect size of 2.3 (Cohen's D) after one week, which remained at 2.4 after 12 months.[16,17]

Each of these studies had numerous limitations, including small sample sizes and limited ability to blind what can be an intense experience on psilocybin. Nonetheless, the effect sizes were large, especially compared to SGA and CBT, which have an average effect size around 0.3 according to some meta-analyses.[18,19] As researchers conduct more trials and bring this treatment closer to FDA approval, it will be important to consider whether PAT will end up being more cost-effective than the current alternatives. This study aims to do this comparison and outline the conditions under which PAT would be considered a cost-effective first-line alternative to SGA and CBT for patients with newly diagnosed MDD.

2 | Methods

2.1 - Model Overview

A decision analytic model used in previous studies of the cost-effectiveness of treatments for patients with newly diagnosed MDD was replicated for this study.[8] The deterministic Markov model tracks the costs (in 2014 U.S. dollars) and QALYs (quality-adjusted life years) for the average patient over 1- and 5-year time horizons for various treatment approaches. As discussed in previous implementations of this model, the 5-year period captures much of the long term benefits and costs associated with the treatments, without going beyond the range of available outcomes data. The model was evaluated from both the healthcare and societal perspectives. A willingness-to-pay (WTP) threshold of $100,000/QALY was used to determine whether treatments were relatively cost-effective.

The model developed for this study attempts to replicate the results of a previous study on the cost-effectiveness of SGA and CBT, and adds two additional branches: PAT+SGA and PAT+CBT.[8] Figure 1 outlines the model structure. In the SGA and CBT models, patients initiate first-line treatment with either SGA or CBT (first cycle), then transition to remission

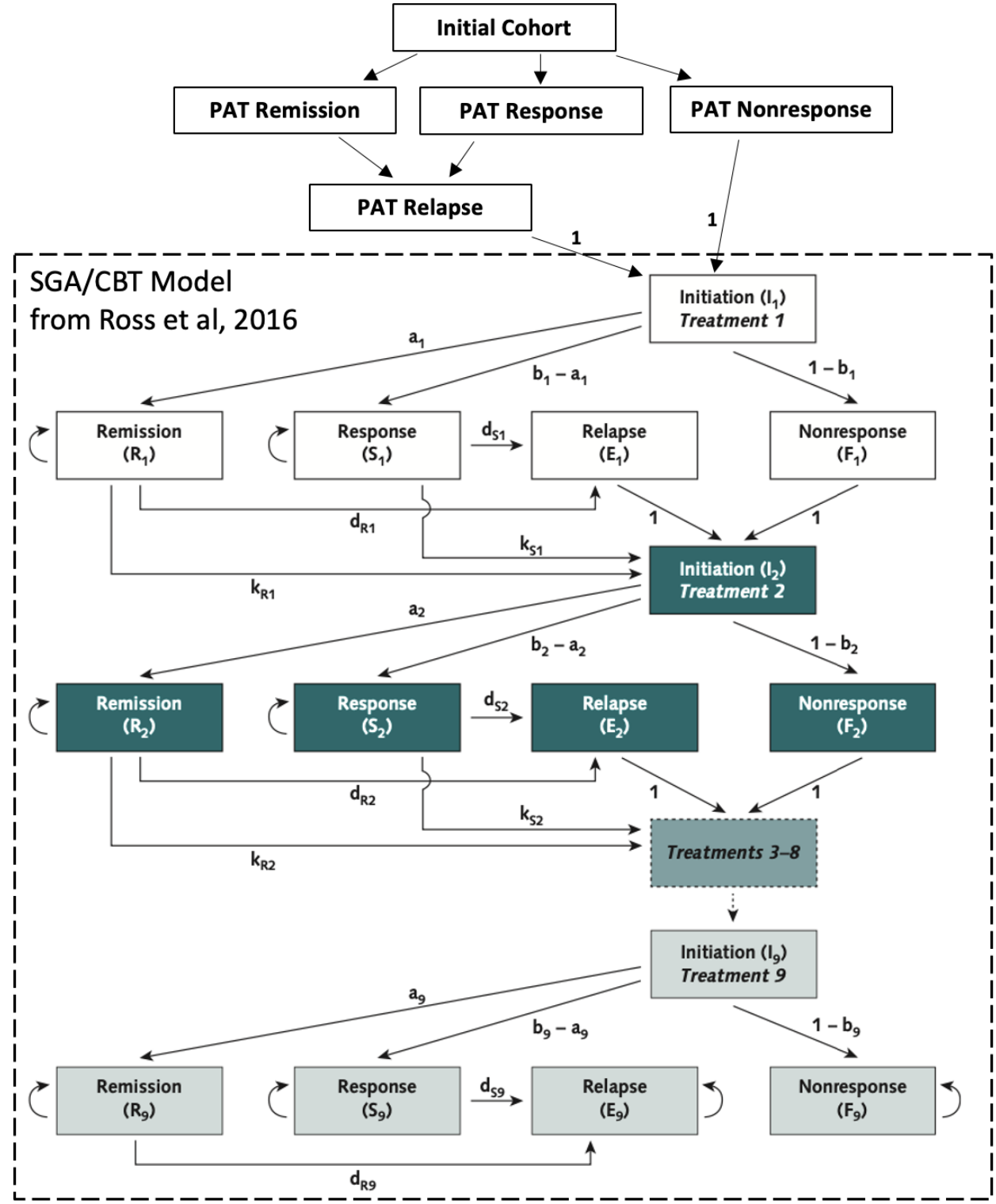
(near-complete recovery of depression), response (partial recovery of depression), or nonresponse. In the following cycles, those in remission and response will either remain in these states, relapse (meaning the depressive symptoms have returned), or discontinue the given treatment due to an adverse event. Patients in the nonresponse or relapse states will move to initiation of the next line of treatment in the following cycle. Those that discontinue from remission or response move directly into initiation of the next line of treatment from the remission or response states, whereas those in nonresponse and relapse essentially wait a cycle before moving on. This process continues for up to nine lines of treatment. If patients relapse or are nonresponsive to the ninth line of treatment, then they remain in those states until the end of the simulation. There is also some constant probability that patients will die in every state, although this is left out of Figure 1 for simplicity.

The PAT+SGA and PAT+CBT branches of the model are very similar, except they assume that patients begin the simulation with a treatment of PAT before moving on to the nine lines of SGA or CBT. Patients are initially split into remission, response, or nonresponse states based on these input probabilities for PAT (discussed below). Patients in remission and response will either remain in these states or transition to the relapse state. It is assumed that there is no discontinuation event for PAT because there is no evidence that an adverse event could occur due to PAT months after the treatment took place.[20,21] Those in the nonresponse and relapse states transition to the initiation of the first-line treatment of SGA or CBT in the following cycle, then proceed as though they were in the SGA or CBT branches of the model.

2.2 - Model Inputs

Table 1 presents all of the base case model input parameters, ranges, and sources. The cycle length is 1 month, which ensures that patients do not move on to another line of SGA/CBT treatment before spending at least two months trying the prior line. All of the annual transition probabilities were converted to monthly probabilities within the model. An annual discount rate of 3% was applied to future costs and QALYs and a half-cycle correction was implemented.[22]

Figure 1 | Model Structure



PAT = psychedelic-assisted therapy; The transition variables (a-d) are defined in Ross et al, 2016[8]

The prior study of SGA and CBT cost-effectiveness derived its estimates of remission, response, relapse, and discontinuation probabilities from multiple meta-analyses and individual studies.[4,5,8] Note that remission is a subset of response (i.e. everyone who meets the criteria for remission has also met the criteria for response, but not vice versa). They also referenced the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial to define the cohort demographics, mortality rate, and subsequent treatment remission and response probabilities.[8,23] The cohort is assumed to be 62.2% women with a mean age of 40.7 years (SD = 13.2).

The utility values were derived from prior studies of patients treated for MDD and were consistent with estimates from clinical trials.[8,24–26] The utility of remission is 0.85, response is 0.72, and nonresponse, relapse, and initiation are 0.58.

Table 1 | Model Input Data

Variable	Base Case (Sensitivity Range)
General inputs, %	
Annual discount rate	3 [8,22]
Annual mortality probability	0.479 [8,18,23,27]
First-line treatment variables	
Initial remission probability	
PAT Prob(Remission | Response), %	0.35/0.60 (0 - 100) [16]
SGA, %	39.7 [8,28]
CBT, relative risk vs. SGA	1.02 [4,8]
Initial response probability	
PAT, %	60 (0 - 100) [16]
SGA, %	63.1 [8,28]
CBT, relative risk vs. SGA	1.11 [4,8]
Annual relapse probability	
PAT, %	38.1 (0 - 100) [16]
SGA, %	38.1 [8,29]
CBT, relative risk vs. SGA	0.73 [4,8,30,31]
Annual discontinuation due to adverse event probability	
SGA, %	24.9 [4,8,32–34]
CBT, relative risk vs. SGA	0.4 [4,8]

Subsequent treatment variables	
Initial remission probability (relative risk vs. first-line SGA)	
Treatment 2	0.93 [8,23]
Treatment 3	0.77 [8,23]
Treatment 4	0.35 [8,23]
Treatments 5–9*	0.33 [8,23]
Initial response probability (relative risk vs. first-line SGA)	
Treatment 2	0.77 [8,23]
Treatment 3	0.48 [8,23]
Treatment 4	0.27 [8,23]
Treatment 5–9	0.26 [8,23]
Annual relapse probability, %	38.1 [8,29]
Annual discontinuation due to adverse event probability, %	24.9 [4,8,32–34]
Utility with depression	
Remission	0.85 [8,26]
Response	0.72 [8,26]
Nonresponse, relapse, initiation	0.58 [8,26]
Costs, $	
First-line treatment, per month	
PAT, month 1	5000 (500 - 10,000) [9]
SGA, months 1–3	76 [8,35]
SGA, months 4+	28 [8,35]
CBT, months 1–3	280 [8,36]
CBT, months 4+	140 [8,36]
Other depression, per year	
Treatment 1	6,747 [8,37]
Treatment 2	8,471 [8,37]
Treatment 3	8,913 [8,38]
Treatment 4	12,862 [8,38]
Treatment 5	12,753 [8,38]
Treatment 6	14,688 [8,38]
Treatment 7	15 984 [8,38]
Treatment 8	16,998 [8,38]
Treatment 9	18,185 [8,38]
Indirect (productivity), per year	
Remission	2,099 [8,39]
Response	5,848 [8,39]
Nonresponse, relapse, initiation	11,755 [8,39]

CBT = cognitive behavioral therapy; SGA = second-generation antidepressant, PAT = psychedelic-assisted therapy.

The reference study did a microcosting analysis to estimate the monthly costs of SGA and CBT for the first few months of the first-line treatment. They also estimated other healthcare costs, stratified by number of prior treatments, based on a study of MarketScan insurance claims for people with depression. For treatments after the first-line, SGA and CBT costs are wrapped into the "other healthcare costs" rather than being microcosted.[8,37,38] Finally, they accounted for the societal perspective by including costs due to lost earnings from depression-related productivity losses as well as time lost from attending physician and therapy appointments.[8]

Due to the nascent nature of PAT research, the base case parameters associated with this treatment are highly uncertain and were therefore estimated conservatively. The most recent study of PAT found the remission and response rates to be 58% and 75%, respectively, after 12 months.[16] For the base case, these parameters were decreased to 35% and 60%, which are lower than the corresponding rates for first-line SGA. This study also found no overall relapse among the patients, however, the same annual relapse probability for SGA (38.1%) was applied to those in the remission or response states for PAT in the base case.[8,16] Very little data is available on the overall cost of a PAT session(s), however, Usona, a company currently working on drug development for psilocybin, told researchers at Founders Pledge that they predict the average cost to be $3,000.[9] This was rounded up to $5,000 for the base case. The other healthcare costs associated with those on first-line depression treatment and annual societal costs were also applied to those in the PAT Markov states.

2.3 - Model Validation

The model was validated by comparing the outcomes from the prior study of SGA and CBT to the outcomes of the corresponding branches in this study. These outcomes included costs, QALYs, and CBT vs. SGA ICERs at the 1- and 5-year time horizons, from both the healthcare and societal perspective. Since the study found CBT to be cost-saving over 5 years, net monetary benefit (NMB) was used as the validation metric for these cases instead of an ICER.

2.4 - Model Outcomes and Sensitivity Analysis

Similar to the prior study, the outcomes measured for this study included the costs, QALYs, and ICERs across the four treatment paradigms at the 1- and 5-year time horizons, from both the healthcare and societal perspective. One- and two-way sensitivity analyses were performed on the following PAT parameters: response rate, fraction of response patients that enter remission, relapse rate, overall treatment cost, and number of cycles (months). Wide ranges of values for these parameters were explored (see Table 1) in order to characterize the approximate conditions under which PAT would be considered cost-effective as a first-line treatment.

3 | Results

3.1 - Model Validation

Table 2 reports the model results for the SGA and CBT branches compared to the results from the prior study (Ross et al 2016) across the different scenarios, perspectives, and outcome metrics.[8] The percent differences for QALYs and costs from both the healthcare perspective and societal perspective were smaller over the 5-year time horizon than over 1-year for both SGA and CBT. This may be due to some programming differences in the early model states. None of the percent differences for QALYs and healthcare costs were greater than 5%. Costs from the societal perspective, however, showed significantly larger discrepancies. The reference study did not provide great detail on how these costs were applied, so it is difficult to know what caused these differences. The difference in the 1-year healthcare perspective ICER was remarkably small (-0.79%), while the difference for the 1-year societal perspective ICER was quite large (-135.64%). The 5-year net monetary benefit differences were also larger than ideal. Based on this assessment, it appears the results from the healthcare perspective and the 5-year time horizon may be more reliable than the counterpart models, although this is speculative.

Table 2 | Model Validation Results

Treatment	Time-Horizon	Measure	Model	Ross et al 2016[8]	Difference	% Difference
SGA	1-Year	HC Cost	$7,772	$8,100	-$328	-4.22%
		SOC Cost	$13,335	$14,600	-$1,265	-9.49%
		QALYs	0.693	0.708	-0.015	-2.18%
	5-Year	HC Cost	$55,676	$57,200	-$1,524	-2.74%
		SOC Cost	$87,141	$90,100	-$2,959	-3.40%
		QALYs	3.230	3.238	-0.008	-0.24%
CBT	1-Year	HC Cost	$8,587	$9,000	-$413	-4.81%
		SOC Cost	$13,880	$16,100	-$2,220	-16.00%
		QALYs	0.700	0.715	-0.015	-2.17%
	5-Year	HC Cost	$54,384	$55,400	-$1,016	-1.87%
		SOC Cost	$83,868	$87,600	-$3,732	-4.45%
		QALYs	3.282	3.293	-0.011	-0.35%
CBT - SGA	1-Year	HC ICER	$118,063	$119,000	-$937	-0.79%
		SOC ICER	$78,933	$186,000	-$107,067	-135.64%
	5-Year	HC NMB	$6,432	$7,300	-$868	-13.50%
		SOC NMB	$8,412	$8,000	$412	4.90%

CBT = cognitive behavioral therapy; SGA = second-generation antidepressant; HC = healthcare; SOC = societal; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit

3.2 - Base Case Results

The results from the base case models are reported in Table 3 and illustrated in Figure 2. The results between the treatment branches were qualitatively similar across the different perspectives, but within the same time-horizons. In other words, over the 1-year time period, PAT+SGA was weakly dominated and PAT+CBT was cost-ineffective compared to CBT alone in both the healthcare and societal perspectives. In this model, CBT was more cost-effective compared to SGA from the societal perspective (ICER = $79,000/QALY) than the healthcare perspective ($118,000/QALY). However, it should be noted that the reference study found CBT to be much less cost-effective from the societal perspective ($186,000/QALY).[8] Over the 5-year period, both perspectives found PAT+CBT to be cost-saving, followed by PAT+SGA, CBT, and SGA.

Table 3 | Base Case Results

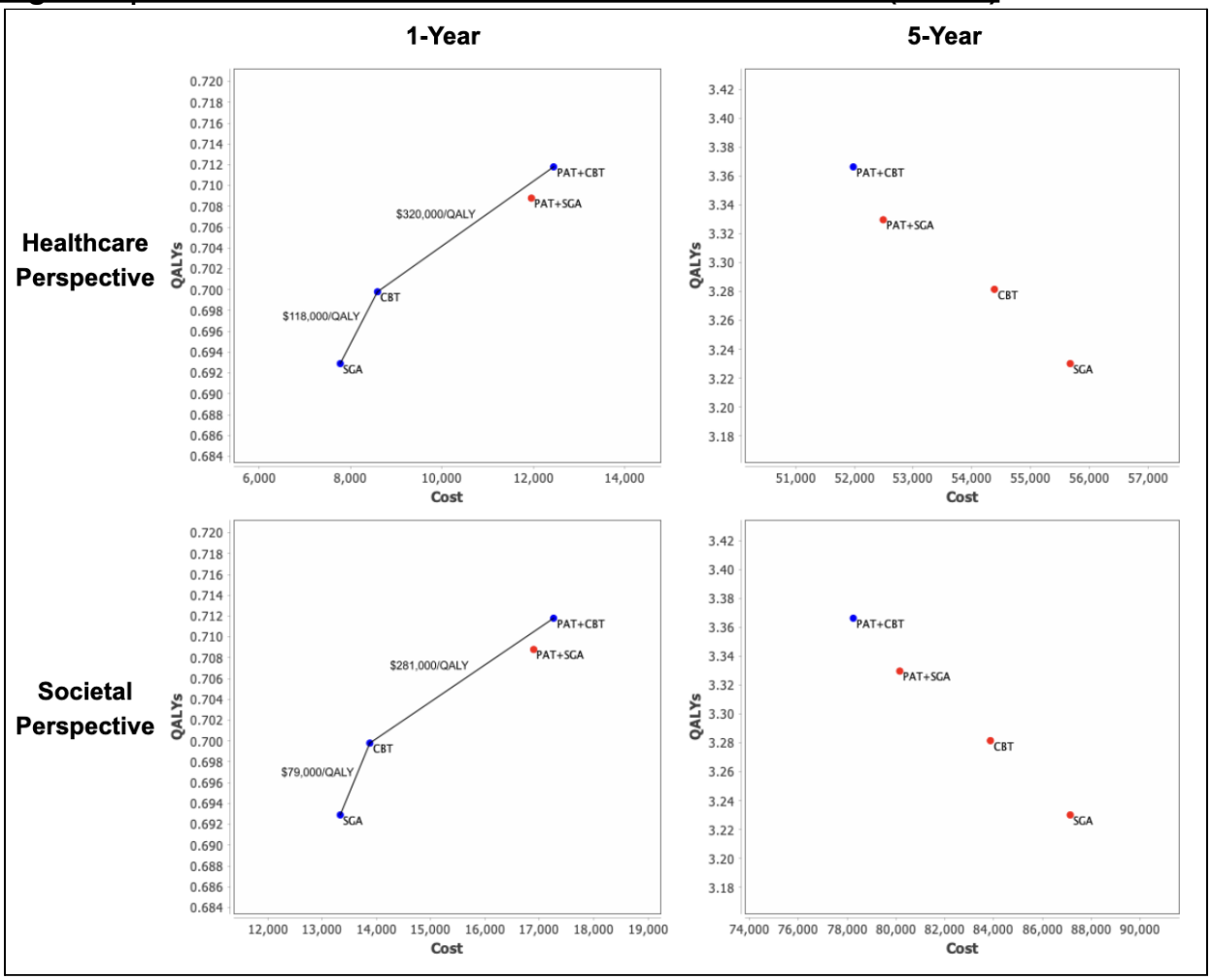
Scenario	Strategy	Cost	QALYs	ICER	Notes
1-Year Healthcare Perspective	SGA	$7,772	0.693	-	Baseline
	CBT	$8,587	0.700	$118,243	Cost-Effective
	PAT+SGA	$11,957	0.709	-	Weakly Dominated
	PAT+CBT	$12,443	0.712	$319,880	Not Cost-Effective
1-Year Societal Perspective	SGA	$13,335	0.693	-	Baseline
	CBT	$13,880	0.700	$79,053	Cost-Effective
	PAT+SGA	$16,897	0.709	-	Weakly Dominated
	PAT+CBT	$17,263	0.712	$280,681	Not Cost-Effective
5-Year Healthcare Perspective	PAT+CBT	$51,979	3.389	-	Cost-Saving
	PAT+SGA	$52,491	3.330	-	Strongly Dominated
	CBT	$54,384	3.282	-	Strongly Dominated
	SGA	$55,676	3.230	-	Strongly Dominated
5-Year Societal Perspective	PAT+CBT	$78,246	3.366	-	Cost-Saving
	PAT+SGA	$80,151	3.330	-	Strongly Dominated
	CBT	$83,868	3.282	-	Strongly Dominated
	SGA	$87,141	3.230	-	Strongly Dominated

CBT = cognitive behavioral therapy; SGA = second-generation antidepressant; PAT = psychedelic-assisted therapy; QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio

3.3 - Sensitivity Analyses

The 1- and 5-year base case analyses clearly indicate that the relative cost-effectiveness of these treatment approaches changes significantly over time. The first sensitivity analysis, shown in Figure 3, ranged the time horizon from 6 months to 6 years and tracked cumulative healthcare costs and QALYs for each treatment branch. The PAT approaches are much more expensive in the beginning due to the high initial cost of PAT, but end up saving costs after approximately 38 months (dashed line). The PAT treatments also have marginally higher QALYs and this difference grows over time. Due to the high degree of uncertainty regarding how the reference study applied costs from the societal perspective and how these costs should be associated with PAT, the sensitivity analyses were only performed from the healthcare perspective.

Figure 2 | Base Case Incremental Cost-Effectiveness Ratios (ICERs)

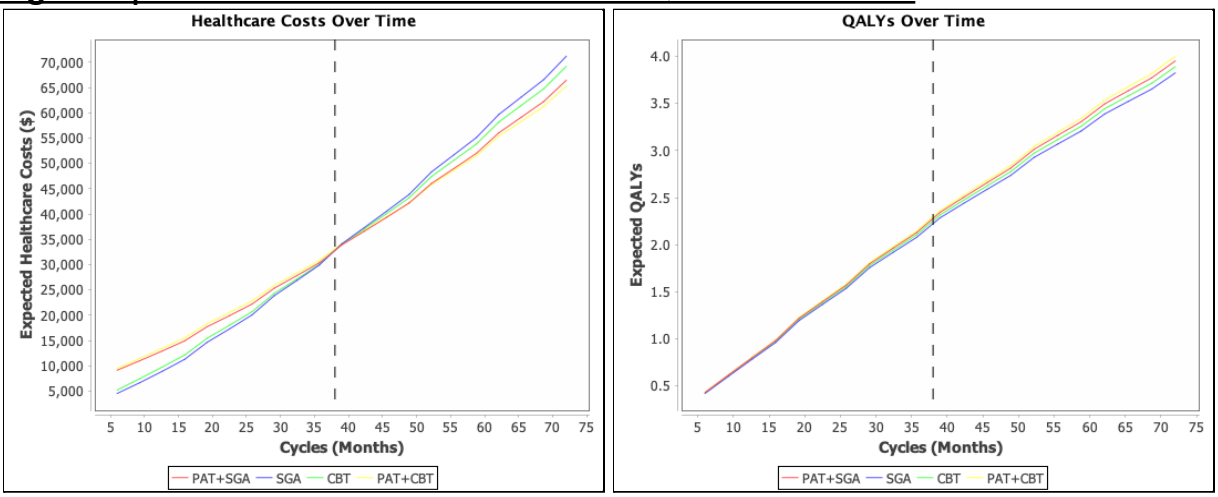


CBT = cognitive behavioral therapy; SGA = second-generation antidepressant; PAT = psychedelic-assisted therapy; QALYs = quality-adjusted life years

Multiple two-way sensitivity analyses were performed over different time horizons to evaluate how various PAT parameters influenced cost-effectiveness. The top-left panel in Figure 4 shows that in the 1-year time frame, PAT would need to be significantly less expensive and have a lower relapse rate for PAT+SGA to be considered cost-effective compared to SGA at a $100,000/QALY WTP threshold. Similarly, PAT would need to have a higher overall response rate and a higher probability of remission given response to make PAT+SGA cost-effective over one year. The corresponding charts for the 5-year time period tell a different story, however. Here, the options involving SGA leave the picture, and PAT+CBT appears robustly cost-effective

compared to CBT. The probability of remission given response for PAT appears to have little influence over the cost-effectiveness in this time period, but other factors remain relevant.

Figure 3 | Treatment Healthcare Costs and QALYs Over Time



CBT = cognitive behavioral therapy; SGA = second-generation antidepressant; PAT = psychedelic-assisted therapy; QALYs = quality-adjusted life years; The dashed line at 38 months represents the approximate time at which the costs of each treatment intersect

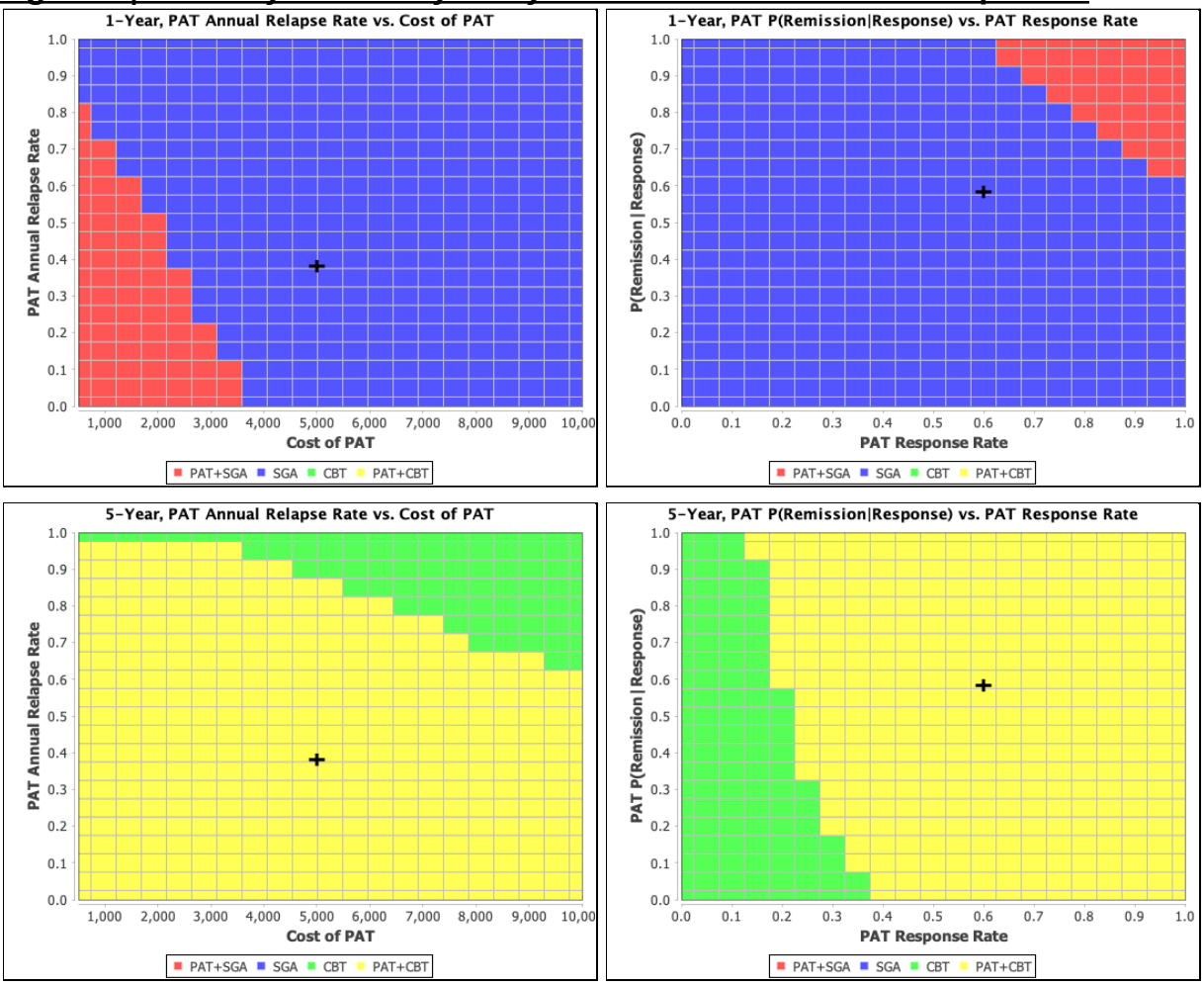
4 | Discussion

By applying prospective, yet conservative estimates for the costs and efficacy of psychedelic-assisted therapy (with psilocybin), this study was able to estimate the potential cost-effectiveness of PAT as a first-line treatment for patients with newly diagnosed major depressive disorder. A decision analytic model from a prior study of SGA and CBT was replicated and validated, then expanded to model PAT.[8] The model validation was not perfect, although it is unclear whether the discrepancies were due to structural differences or parameter value differences. Either way, the model appeared to behave in a reasonable manner, particularly for measuring QALYs and costs from the healthcare perspective.

Under base case conditions, PAT+SGA and PAT+CBT were not considered cost-effective over the first year of the simulation, but became cost-saving compared to SGA and CBT alone over 5 years. A sensitivity analysis of the number of cycles suggested that PAT options became cost-effective within the first 2-3 years. Additional sensitivity analyses showed

that PAT+SGA would only be cost-effective in the short term under optimistic parameter assumptions, but PAT+CBT appeared robustly cost-effective in the longer term.

Figure 4 | Two-Way Sensitivity Analyses from the Healthcare Perspective



CBT = cognitive behavioral therapy; SGA = second-generation antidepressant; PAT = psychedelic-assisted therapy; The "+" indicates the base case parameters; Willingness-to-pay threshold = $100,000/QALY

4.1 - Limitations

This study had numerous limitations. First of all, research on PAT is still quite preliminary and limited to a handful of trials with small sample sizes. Therefore, each of the parameters had to be approximated, but they were estimated conservatively to account for a potential positive bias coming from early trials. The wide ranging sensitivity analyses on these parameters also aimed to account for this uncertainty. Notably, however, this study did not include a probabilistic

sensitivity analysis, as the distributions of these parameters are also highly unknown at this time.

As mentioned previously, the model validation indicated that the model used in this study did not perfectly match the model used in the reference study. Since the cause of the discrepancies are unknown, the direction in which this may have biased the results is also unknown. The societal costs in particular were under defined, and it would have been difficult to measure the societal costs associated with PAT.

The referenced model had its own assumptions and limitations.[8] For example, the model assumes that everyone who goes into remission or response from a treatment will eventually relapse, although this seems unlikely to be true. It also assumes that patients entering the remission or response states continue spending the same amount on healthcare as those for whom treatments are ineffective. Their analysis was based on patients with newly diagnosed MDD, who may respond differently to new treatments than those with long-standing MDD. Of course, the PAT studies were also not based on patients with newly diagnosed MDD, so it is not clear how these trial results would generalize to this patient population.

4.2 - Future Work

Further work in improving the validity of this model would help reduce the uncertainty of the results presented. A probabilistic sensitivity analysis could be valuable in characterizing the range of outcomes associated with PAT and the likelihood of it being cost-effective. A value of information analysis would also be useful for researchers designing trials of PAT. Modeling of the effects of different psychedelic drugs, such as MDMA, on different mental health conditions, such as PTSD, would be another important line of future work on this topic.

5 | Conclusion

Based on the success of recent trials of PAT for treating patients with various forms of depression, this innovative method could prove to become an integral aspect of mental

healthcare in the future. This study suggests that PAT has the potential to not only be more efficacious, but less expensive in the long run as well. This should give hope to policymakers, public health officials, mental health practitioners, and those suffering from depression, however, much more clinical research, modeling, and legal work needs to be completed before PAT can enter the standard mental healthcare paradigm.

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