Article

Modelling Treatment Pathways in Treatment-Resistant Depression: The Impact of Nasal Esketamine on Cost-Effectiveness, Waiting Times and Patient Outcomes

Julia Bertsch [3,*], Madalina Fron [4,*], Ellen Heck [5,*], Tom Kitak [4,*], Marcello Pepe [6,*], Joey van Zanten [7,8,*]

[1] Nanobiology, Department of Bionanoscience, Faculty of Applied Science (AS), TU Delft, Van der Maasweg 9, Delft, 2629HZ, the Netherlands; I.C.Alecu@student.tudelft.nl
[2] Nanobiology, Erasmus MC, Dr. Molewaterplein 60, Rotterdam, 3015GJ, the Netherlands
[3] Aerospace Engineering, Faculty of Aerospace Engineering (AE), TU Delft, Kluyverweg 1, 2629 HS Delft, the Netherlands; J.S.Bertsch@student.tudelft.nl
[4] Computer Science and Engineering, Faculty of Electrical Engineering, Mathematics and Computer Science (EEMCS), TU Delft, Mekelweg 4, Delft, 2628CD, the Netherlands; O.M.Fron-1@student.tudelft.nl; T.Kitak@student.tudelft.nl
[5] Psychology, Faculty of Psychology and Neuroscience (FPN), Maastricht University, Universiteitssingel 40, Maastricht 6229ER, the Netherlands; ellen.heck@student.maastrichtuniversity.nl
[6] Psychology, Faculty of Social and Behavioral Sciences, Leiden University, Wassenaarseweg 52, Leiden 2333AK, the Netherlands; s3183810@vuw.leidenuniv.nl
[7] Molecular Science and Technology, Department of Biotechnology, Faculty of Applied Science (AS), TU Delft, Van der Maasweg 9, Delft, 2629HZ, Netherlands
[8] Molecular Science and Technology, University of Leiden, Einsteinweg 55, Leiden, 2333CC, Netherlands; J.M.H.vanZanten@student.tudelft.nl
* These authors contributed equally to this work.

Abstract: Treatment-resistant depression (TRD) poses a growing challenge with profound societal ramifications. While individual medical interventions have demonstrated promise in clinical trials, their efficacy alone is insufficient for successful implementation. An equally critical consideration is the economic viability of a new treatment, along with its broader impact on the existing treatment landscape. This study evaluates intranasal esketamine within the Dutch depression care model, employing both a hybrid of agent-based modeling (ABM) and system dynamics (SD) as well as a novel approach unifying both techniques, to assess its viability as an additional treatment option for TRD. Our analysis indicates that while esketamine incurs higher initial costs than current treatments, its integration could enhance patient outcomes, decrease wait times, and ultimately reduce long-term societal expenses. However, our findings are limited by the data available, with no real-world dataset comprehensive enough to validate our model. Esketamine emerges as a promising, cost-effective treatment option for TRD, though its full potential is contingent on further research due to the current limitations in data for model validation. The absence of extensive real-world datasets underscores the need for additional studies to confirm these preliminary findings.

Keywords: Treatment-Resistant Depression, Health Economics, Mental Healthcare Systems, Economic Modelling, Esketamine

Citation: Bertsch, J.; Fron, M.; Heck, E.; Kitak, T.; Pepe, M.; van Zanten, J. Modelling Treatment Pathways in Treatment-Resistant Depression: The Impact of Nasal Esketamine on Cost-Effectiveness, Waiting Times and Patient Outcomes. *Preprints* **2024**, *1*, 0.

1. Introduction

Major Depressive Disorder (MDD) affects approximately 6.7% of the global population, leading to symptoms such as persistent sadness, lack of interest, suicidal thoughts, and other cognitive and physical issues, significantly impairing life quality [1,2]. In the Netherlands, depression rates have been rising since the early 2000s, with nearly 20% of the population showing depressive symptoms, causing MDD-related healthcare costs to triple from 2003 to 2015 [3,4]. Despite available treatments, around 30% of MDD patients experience Treatment-Resistant Depression (TRD), not achieving remission after several first-line treatments [5].

TRD, characterised by inadequate response to at least two antidepressants at proper doses and durations, poses a significant treatment challenge. Its management often requires

a step wise approach, beginning with medication optimisation and possibly including further pharmacotherapy or psychotherapy. In cases of persistent non-response, more intensive treatments like ECT may be employed. The absence of a standardised treatment protocol leads to varied care experiences and potentially prolonged, costly inpatient treatment. This variability exacerbates patient suffering, extends depressive episodes, and increases healthcare and societal costs [6–8]. There's a clear need for a standardised treatment pathway to address these issues and enhance TRD patient care [9].

Esketamine, an NMDA receptor-targeting intranasal formulation [10], offers rapid antidepressant effects and potential to lessen suicidal thoughts. Clinical trials have demonstrated significant improvements in patients within hours to days of administration, positioning it as a valuable option between augmentation therapies and ECT. However, the high cost of esketamine, approximately €10 000, raises concerns about its economic viability for widespread use in healthcare systems.

This study aims to evaluate esketamine's integration into the Dutch TRD treatment protocol, focusing on whether its clinical advantages outweigh its high costs against TRD's societal and economic impacts. Additionally, it seeks to develop and analyse two simulation models to reflect the complexities of TRD treatment and healthcare system dynamics.

We developed two simulation models to analyse healthcare dynamics. The Hybrid ABSD model combines System Dynamics (SD) and Agent-Based Modelling (ABM) to assess both broad healthcare system impacts and individual patient behaviours, offering a detailed view of how healthcare changes affect the overall system and patient experiences. While effective, this model struggles with scaling for larger, more complex scenarios. However, its effectiveness in modelling healthcare dynamics is well-supported by existing literature [11].

To overcome these limitations, we introduce the ADES (Agent-based Discrete Event Simulation) model, merging ABM's individual-level focus with Discrete Event Simulation's (DES) process-oriented approach. ADES is adaptable to various data types and healthcare scenarios, featuring a decision-making tree for outlining treatment paths and an event timing system for coordinating healthcare events. This model's complexity and need for extensive validation pose challenges but enhance its relevance to diverse policy questions.

These models aim to elucidate the effects of integrating new treatments like esketamine into existing healthcare systems, providing valuable insights for healthcare policy and treatment protocol development.

2. Methodology

2.1. Treatment Pathway and Underlying Model Architecture

In this study, we anchor our models within the framework of stepped-care guidelines prevalent in the Netherlands for the management of depression, with an emphasis on the treatment modalities for TRD as delineated by Spijker et al. (2022). The management of TRD typically commences with augmented therapies, including antidepressants and antipsychotics. Should these interventions prove ineffective, Electroconvulsive Therapy (ECT) may be considered as an alternative option. The absence of a standardized TRD treatment pathway results in diverse clinical practices, largely influenced by individual psychiatrist preferences and clinical judgment, as observed by Gillain et al. (2022). Our model's incorporation of these therapies is informed by their prevalent use as noted by Peeters et al. (2016), acknowledging the personalized nature of TRD management that can differ substantially from one psychiatrist to another.

The prevailing legal stipulations within the Dutch healthcare system necessitate the undertaking of at least one course of augmented therapy prior to the contemplation of esketamine as a treatment option. In light of this, our proposed model introduces a treatment pathway that integrates esketamine as an intermediate step following the initial augmented therapy phase and preceding the potential employment of ECT. This modification is motivated by the emerging body of evidence supporting the efficacy of esketamine

in addressing TRD, providing an alternative for patients who exhibit sub-optimal responses to traditional augmented therapies.

Figure 1 depicts the treatment pathway under esketamine therapy. Patients progress through various treatment options, with the potential for remission upon successful treatment. In remission, a relapse function determines the risk and timing of relapse, while recovery begins after 24 weeks. Recovered patients cease medication but may still face relapse, with the relapse function guiding further steps. Those without relapse in recovery remain until the simulation's end, offering insights into esketamine's impact on patient outcomes.

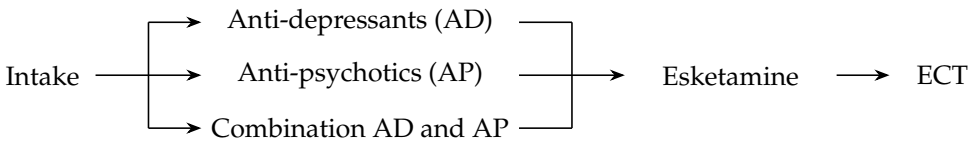


Figure 1. Underlying treatment pathway used in both models for the implementation of esketamine

Following the initial assessment, patients are placed on a waiting list and subsequently admitted to specific treatment programs as capacity becomes available. The duration of each treatment program is pre-defined, and upon its completion, patients may follow one of three distinct trajectories: "response," "remission," or "treatment failure." In the event of a "response," the patient proceeds to undergo the same treatment once more. "Remission" signifies the patient's successful exit from the treatment pathway, while "treatment failure" leads to the patient being re-enrolled on a waiting list for subsequent therapeutic interventions.

Patients who maintain a state of "remission" for a duration exceeding six months are classified as "recovered." It is essential to note that patients in both "remission" and "recovery" phases remain at risk of experiencing a relapse. Those who do relapse are re-introduced into the initial phase of the treatment pathway for further intervention.

2.2. Data Collection

To construct an accurate representation of the existing treatment pipeline, an extensive literature review was undertaken to identify essential data points. Data was extracted from publicly available research papers, excluding any sensitive information. The data collection period spanned from December 2023 to January 2024, encompassing historical materials published before January 15, 2024. The gathered data was categorized into three primary domains: clinical data, hospital data, and cost-effectiveness data. The cost-effectiveness domain focused on quantifying the treatment's utility, while clinical and hospital data described the quantification of depression severity, treatment progression, and treatment capacities, respectively. A comprehensive list of key terms and parameters is summarized in Table 1, while the exact parameter values can be found in Table A1, Table A2, and Table A3.

Clinical data pertaining to remission, relapse, response rates, and treatment durations were drawn from prior clinical trials. Specifically, this study relied on data derived from trials involving adult individuals aged 18 to 65. Preference was given to studies with substantial sample sizes, including trials with participant counts of n = 97 (National Library of Medicine [NLM], NCT02417064), n = 98 (National Library of Medicine [NLM], NCT02418585), n = 273 (National Library of Medicine [NLM], NCT02493868), n = 580 (National Library of Medicine [NLM], NCT02497287), n = 172 (National Library of Medicine [NLM], NCT03113968), n = 203 (National Library of Medicine [NLM], NCT04338321), and n = 56 (National Library of Medicine [NLM], NCT01687478). Furthermore, these clinical trials were conducted between 2012 and 2020, providing recent and reliable sources of data.

Remission is defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of 12 or less after four weeks of treatment (Quilty et al., 2013). A response to treatment is indicated by a reduction in the MADRS score of at least 50%, whereas relapse

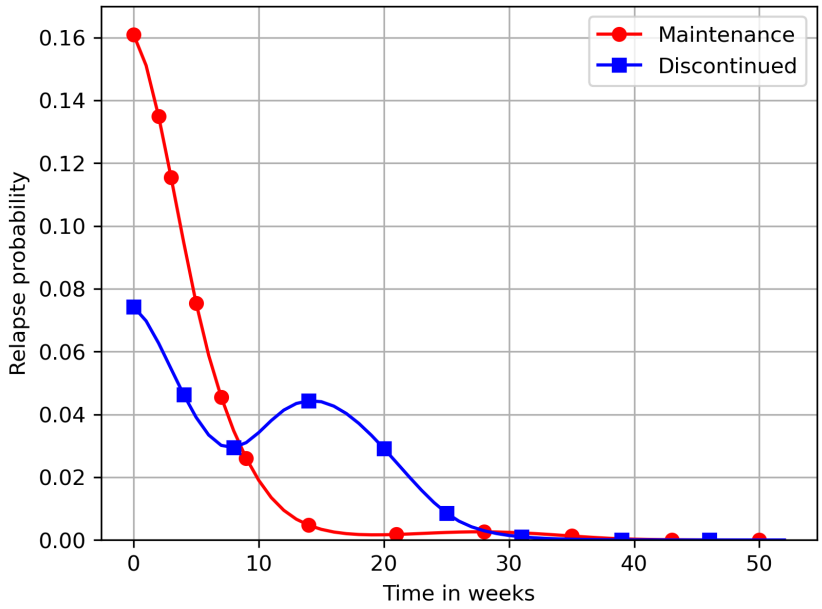


Figure 2. p

refers to the return of depressive symptoms in a patient who had previously achieved remission (Quilty et al., 2013). Given that available data on relapse rates were discrete and had limited temporal resolution, a continuous, smoothed relapse function was developed to mitigate the simultaneous occurrence of numerous relapses. The foundation for these functions relies on clinical data acquired through the Patient Health Questionnaire-9 (PHQ-9) as presented by Duffy et al. (2021), where an elevated PHQ-9 score of 5 or more is indicative of a heightened risk of relapse. Followingly, data resulting from a simulation encompassing a thousand patients over the course of a year generated a probability graph providing the likelihood of relapse. For this study, two relapse functions were employed: (a) a maintenance relapse function including patients who are still following a medication regimen, (b) a discontinuation relapse function referring to patients who do not take medication anymore. Subsequent refinements were made to the relapse function based on these findings, depicted in Figure 2.

The hospital dataset concerns key parameters such as capacity, initial patient count, and patient flow. The estimation of treatment capacity is grounded in the total number of psychiatrists at the Erasmus Medical Center (EMC), with a conservative assumption that each psychiatrist can schedule an average of 2.5 patients per week, resulting in a total weekly capacity of 50 patients. To gauge the number of patients with Treatment-Resistant Depression (TRD), population data from Zuid-Holland, sourced from the Centraal Bureau van Statistiek (CBS), was employed. This estimation takes into account a MDD prevalence of 6.7% and a TRD occurrence rate of 30%. The initial patient count in the simulation is adjusted based on the ratio of EMC-employed psychiatrists to the total number in Zuid-Holland.

To project the inflow of patients to the EMC, historical data on the population and birthrate of Zuid-Holland spanning the years 1981 to 1987 was analyzed. This period aligns with the birth years for the average age at which a typical TRD patient experiences their first depressive episode. Using the same prevalence rates and population data from 2023, we estimated the total number of patients and converted it into new patients per week. Additionally, a decision tree model was formulated to predict the distribution of treatment allocation percentages. The model's scoring method relies on the Dutch Measure of Quantification of Treatment-Resistant Depression (DM-TRD), offering guidance for the allocation of augmented therapies during the initial intake process (Peeters et al., 2016).

The cost-effectiveness data includes three key parameters: Quality of Life (QOL), direct costs, and indirect costs. QOL weights were derived from a comprehensive synthesis by Mrazek et al. (2014), combining QOL weights from four distinct studies that utilized both Standard Gamble and EQ-5D methods. This approach generated average QOL estimates for patients with different treatment outcomes, including remission, response, and no response. The QOL weight for patients in remission was assumed to be identical to that of the healthy population of individuals aged 30-39 (Sullivan and Ghushchyan, 2006). Total costs were split into direct and indirect costs. Direct costs encompass cost for medication, intake and maintenance session cost. Medication costs were obtained from the Zorginstituut Nederland (n.d.). Intake and maintenance session costs for esketamine treatment were obtained directly from Janssen. Intake and personnel costs per maintenance session were assumed to be identical across all treatments. Frequency of sessions and dosage were obtained from the respective clinical trials. Indirect costs encompass the cost of lost productivity and the cost of health benefits and were calculated using unemployment rates for patients in response / no response and patients in remission that were obtained from McCrone et al. (2018), the average gross wage of the Dutch population in 2023 (CPB Netherlands Bureau for Economic Policy Analysis, 2023), and a health benefit of 70% of an unemployed patient's most recent gross wage (Netherlands Worldwide, 2024).

Table 1. Comprehensive Overview of Model Parameters: The table presents a detailed compilation of all the parameters utilized in the development of our models. The information is sourced from a variety of academic publications and clinical trials, the latter identified by their unique NCT numbers

Parameters	**Definition**	**Source**
Capacity	The maximum number of patients that can be treated by specialists in an area or facility. We look at the wider Zuid-Holland area, but also EMC specifically	Centraal Bureau van Statistiek
Direct costs	The costs associated with a specific treatment (includes medication cost, intake and set up cost, maintenance session cost)	Zorginstituut Nederland, Janssen
Indirect costs	The cost lost and accumulated due to absenteeism	McCrone et al., 2018; CPB Netherlands Bureau for Economic Policy Analysis, 2023
MADRS	Montgomery-Åsberg Depression Rating Scale, is a psychological assessment tool used to measure the severity of depressive episodes in patients with mood disorders. It consists of ten items, each rated on a scale of 0 to 6	Montgomery and Åsberg, 1979
Number of patients at initial conditions	The intake of patients at the first timepoint	Centraal Bureau van Statistiek
Patient flow per week	The number of patients newly diagnosed with TRD	Centraal Bureau van Statistiek
PHQ-9	Patient Health Questionnaire-9 is a self-report tool designed to assess the severity of depressive symptoms in individuals. It consists of nine questions based on the diagnostic criteria for major depressive disorder outlined in the DSM-5	Duffy et al., 2021
QOL	Quality of life (QOL) is a concept which aims to capture the overall well-being, whether of a population or individual, regarding both positive and negative elements within the entirety of their existence at a specific point in time	Mrazek et al., 2014
Relapse	Patients that are diagnosed with depression again, after remission	NCT04338321; NCT01687478; NCT02493868; NCT02497287; NCT02417064; NCT02418585; NCT03113968
Remission	Patients that show a MADRS total score of ≤ 12 at endpoint (4 weeks post treatment)	Quilty et al., 2013
Response	Patients that show a $\geq 50\%$ reduction in MADRS total score at endpoint (4 weeks post treatment)	Quilty et al., 2013
Treatment Duration	The period of medication intake; can be separated into an induction and maintenance phase	Sapkota et al., 2021b

2.3. Connecting Agent Based Modelling and System Dynamics

Our choice of ABM and SD hinges on the specific requirements behind our objective. ABM proves effective for studying complex adaptive systems marked by self-organisation and adaptation (Levin, 1998). Focused on micro-level interactions, ABM unravels emergent patterns and transient dynamics, accounting for entity heterogeneity, spatial-temporal nuances, and stochasticity. Rather than meticulously reproducing micro-level processes, ABM strategically simulates the minimum functions necessary to replicate system-level behaviours.

Conversely, SD adopts an aggregated approach, representing the entire system through stocks and flows. It emphasises system-level behaviour, elucidating growth through feedbacks and non-linearities (van den Belt, 2004). Differential equations analyse dynamics, while causal-loop diagrams visualise main interactions, aiding in feedback and system dynamics comprehension. Equations derived from these diagrams identify stable states and system properties.

For intricate analyses, simulations with varied parameters and repetitions are essential for both ABM and SD. In addressing links between subsystems, coupling becomes pivotal. While the conventional notion is ABM representing the micro-level and SD the macro level, the coupling order can vary (Swinerd and McNaught, 2012). Coupling options range from subsequent to dynamic coupling. For instance, SD may simulate internal entity processes, while ABM maps interactions (Bradhurst et al., 2015). Alternatively, top-down effects on individual entities can shape emergent properties (Haase et al., 2012).

Recent studies have demonstrated the effectiveness of integrating diverse modelling techniques, particularly the combination of ABM and SD. Notable examples include a study by Brice et al. (2023), where the authors jointly modelled disease progression and treatment pathways for depression using both ABM and SD, offering a nuanced understanding of the complex dynamics involved in mental health conditions. Stapelberg et al. (2021) presented a Discrete-Event, Simulated Social Agent-Based Network Transmission (DESSABNeT) model for communicable diseases, showcasing the versatility of hybrid models in capturing the dynamics of disease transmission, which is relevant to mental health research where social factors play a crucial role. Building on these related studies, our current research contributes to the expanding body of knowledge on the application of hybrid modelling in mental healthcare.

2.4. Hybrid ABSD

The Hybrid ABSD model integrates two distinct models: an ABM model for patients with TRD and an SD model for the TRD treatment pathway. These models operate concurrently, synchronising data at weekly intervals. In this framework, every "stock" within the SD model correlates with a state in the ABM model, denoting the agent's current position within the SD structure and the agent's behaviour. The ABM model tracks the medical history of each patient, which is analysed in post-processing. Architecture diagram of Hybrid ABSD model can be found in Figure A1.

The model is implemented with Python 3.10 and relies on the computational modelling framework Business Prototyping Toolkit for Python to build SD and ABM simulation models. The codebase for the ABSD model is publicly available in the associated GitHub repository (Kitak & Fron, ABSD 2024).

2.5. Hybrid ADES

In developing the ADES (Agent-Based Discrete Event Simulation) model, we expand our analytical framework to incorporate the precision of discrete event simulation (DES) within an agent-based modelling context. Unlike the ABSD model, which operates ABM and SD concurrently yet separately, ADES seamlessly integrates ABM with DES into a singular, cohesive framework. This integration allows for a more granular examination of individual patient journeys through the healthcare system while efficiently managing event sequencing and timing. DES offers a powerful approach to modelling, focusing on

the occurrence of events in a system and their impact on the state of entities within it. By integrating DES, the ADES model gains the ability to meticulously track and analyse the sequence of treatment-related events for each patient agent, enhancing the model's ability to simulate complex healthcare pathways. The model's event timing system significantly improves runtime efficiency by optimising the scheduling and execution of events, thereby reducing computational overhead. This feature ensures that the model remains scale-able and adaptable to various healthcare scenarios, making it a useful tool for policy analysis and decision-making in mental health care.

The ADES model features a decision tree during the intake phase to guide treatment allocations, evaluating patient profiles based on criteria like MADRS scores, symptom severity, and psychotic symptoms. This method directs patients towards appropriate therapies, such as antipsychotics for those with psychotic symptoms or a combination of antipsychotics and antidepressants for severe depression without psychotic symptoms, attempting to align with clinical practices. This decision tree, serving as a proof of concept, demonstrates the ADES model's ability to mimic complex clinical decisions, generating treatment allocation percentages that enhance the model's relevance and allow for consistency with the ABSD model. While currently simple, this feature sets the foundation for future enhancements to include a wider range of clinical criteria, improving the model's reflection of real-world treatment pathways.

The codebase for this model is publicly available in the associated GitHub repository (Bertsch, Atlas4TRD 2024).

2.6. Data Analysis

Patient outcomes were evaluated by analyzing trends in the proportions of recovery and remission across all treatment pathways. These measures represent the cumulative percentage of patients who achieved recovery or remission up to specific time points. Additionally, we examined trends in the size of the waiting lists over time to evaluate the efficiency and accessibility of each treatment option and pathway.

For the cost-effectiveness analysis, we computed the average Quality-adjusted-life-years (QALYs) for each treatment pathway by multiplying the QOL weight for each health state (remission, response, no response) by the duration a patient spent in the respective health state.

The total cost per patient was estimated from both healthcare (direct costs) and societal (indirect costs) perspectives. To account for societal costs, the study factored in unemployment rates among patients in various health states, serving as proxies for individual unemployment probabilities. These rates were then multiplied by the duration in each health state and 1.7 times the average gross wage in the Netherlands to calculate indirect costs. We further assessed the incremental cost-effectiveness ratio (ICER) to compare the two treatment pathways. The ICER quantifies the additional cost per additional QALY gained by the pathway incorporating esketamine treatment compared to the pathway without esketamine treatment. This ratio is determined by dividing the incremental cost (the difference in total cost per patient between the two pathways) by the incremental effectiveness (the difference in mean QALY per patient between the two pathways). The ICER provides insight into the additional cost required for each additional benefit of one pathway over the other. Additionally, we calculated the net monetary benefit (NMB) using a willingness-to-pay (WTP) threshold of €50,000 per QALY gained (Schurer et al., 2022).

$$NMB = (WTP \times \Delta QALYs) - \Delta Cost \tag{1}$$

Equation 1 represents the NMB calculation, where WTP is the willingness-to-pay threshold per Quality-adjusted-life-year (QALY) gained, $\Delta QALYs$ is the difference in QALYs between two treatment pathways, and $\Delta Cost$ is the difference in total cost per patient between the two pathways. A positive NMB value indicates that the health benefits, in monetary terms, outweigh the intervention's cost, signifying cost-effectiveness.

In our analysis, we placed a particular emphasis on the treatment capacity, with a specific focus on esketamine, as a pivotal parameter. Given our estimated overall treatment capacity of 50 patients at the EMC, we conducted simulations for various scenarios, encompassing a worst-case scenario (5 patients), a base-case scenario (10 patients), and a best-case scenario (20 patients) regarding the capacity for esketamine treatment. We then allocated the remaining patients to alternative treatments based on our estimated capacity distribution percentages. Our objective was to examine the impact of these diverse scenarios on patient outcomes, waiting list sizes, and cost-effectiveness within the healthcare system.

2.7. Validation

While our novel modeling approach, Unified ABSD, represents an advancement in addressing some of the limitations of the existing Hybrid ABSD, it's essential to acknowledge that it remains in the proof-of-concept stage and requires validation.

In this study, we employ a validation strategy for the Unified ABSD model by conducting a comparative analysis with the Hybrid ABSD model. Our validation approach involves assessing patient outcomes (specifically, recovery and remission trends) and tracking waiting list sizes over time. This validation strategy is necessitated by the absence of direct real-world data for validation purposes.

By comparing the results obtained from the Unified ABSD model with those from the Hybrid ABSD model, which differs in architectural design and input handling capabilities, our aim is to establish the validity of the Unified ABSD. Achieving similar results from both models, despite their architectural and methodological distinctions, would serve as evidence of the reliability and accuracy of the Unified ABSD in complex system simulations.

3. Results

The simulations were conducted over an extensive time frame of approximately 14 years, equivalent to 750 weeks. The initial phase, spanning around 7 years or 300-400 weeks, was dedicated to the gradual filling of stocks/treatments and the establishment of stable patient flow, mirroring real-world dynamics. Following this stabilization period, the simulations continued for an additional 7 years.

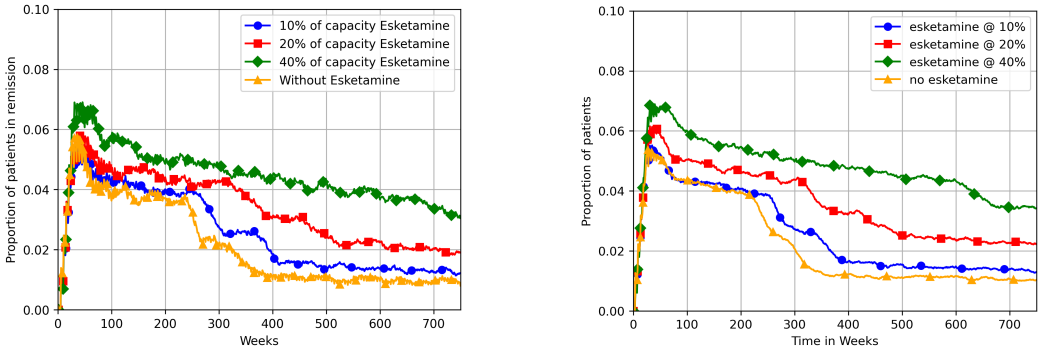
This extensive time horizon was chosen to allow for the observation of long-term trends in our analysis. The simulated population initially consisted of 1156 individuals, with a weekly increase of 1 patient seeking treatment at the EMC.

3.1. Patient outcomes

The trends observed in the proportion of patients in remission and recovery over time, as illustrated in Figure 3 and Figure 4, exhibit significant similarities. Our analysis consistently demonstrates that higher esketamine capacities correspond to a greater proportion of patients achieving recovery.

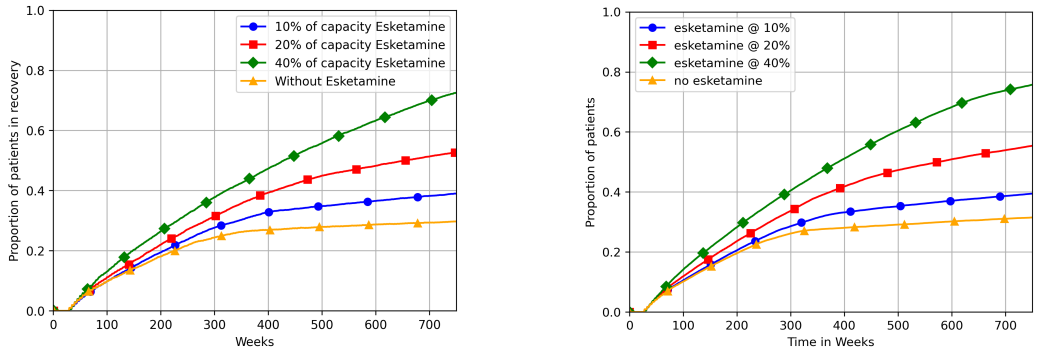
In the Hybrid ABSD model, the recovery proportions without esketamine stabilize at approximately 0.3 after 400 weeks. With a 10% esketamine capacity, this proportion slightly improves to around 0.4 after 700 weeks. The Unified ABSD model exhibits a parallel pattern, albeit with slightly higher recovery rates. In this case, the proportions plateau at approximately 0.35 for scenarios without esketamine and around 0.4 with a 10% capacity scenario. Moreover, for higher capacities (20% and 40%), both models display consistent recovery proportions. The 20% esketamine capacity pathway achieves a recovery proportion of approximately 0.5 after 700 weeks, while the 40% capacity pathway reaches a recovery proportion of about 0.7 within the same timeframe. Notably, as the simulation duration extends, the disparities in recovery rates among pathways with varying esketamine capacities become more pronounced.

Similarly, our analysis indicates that increased esketamine capacities are associated with higher proportions of patients achieving remission in both models. It's noteworthy that even a relatively modest 10% esketamine capacity demonstrates a significant enhancement in remission rates when contrasted with scenarios devoid of esketamine. In both models,



(a) **(b)**

Figure 3. Weekly evolution of proportion of patients in remission. (a) shows remission proportions using Hybrid ABSD and (b) shows remission proportions using Unified ABSD.



(a) **(b)**

Figure 4. Weekly evolution of proportion of patients in recovery. (a) shows recovery proportions using Hybrid ABSD and (b) shows recovery proportions using Unified ABSD.

distinctions in remission rates among varying esketamine capacities become apparent around the 250-week milestone, particularly between the 20% and 40% capacity scenarios. However, after reaching week 700, it appears that the remission proportions for the different capacities begin to converge once more.

3.2. Waiting lists

Figure 5 and Figure 6 illustrate the trends in waiting list sizes in both models. These patterns exhibit remarkable congruence between the two models, marked by analogous steep increases and comparable stabilization rates across various treatment scenarios.

Specifically, at a 10% esketamine capacity, both models show a rapid escalation in waiting list size to approximately 1000 patients by the 400-week mark, followed by a more gradual ascent. When esketamine capacity is set at 20%, both models display stabilization and a subsequent decrease in esketamine waiting list sizes, starting around the 500-week mark. A noteworthy observation across both models is the increase in the waiting list for ECT as esketamine capacity rises. This trend is attributed to a higher absolute number of patients not responding to esketamine and subsequently requiring ECT.

When esketamine capacity reaches 40%, the waiting list for esketamine drops significantly in both models, suggesting that at lower capacities, esketamine availability is a critical factor. Conversely, in scenarios without esketamine, there is a surge in ECT waiting list sizes, exceeding 1200 patients after 600 weeks in both models.

In Figure 7, the absolute number of patients on the waiting list over time, aggregated across all treatments, is illustrated. The graphs underscore that pathways with higher esketamine capacities lead to lower proportions of patients on a waiting list. Notably, at a

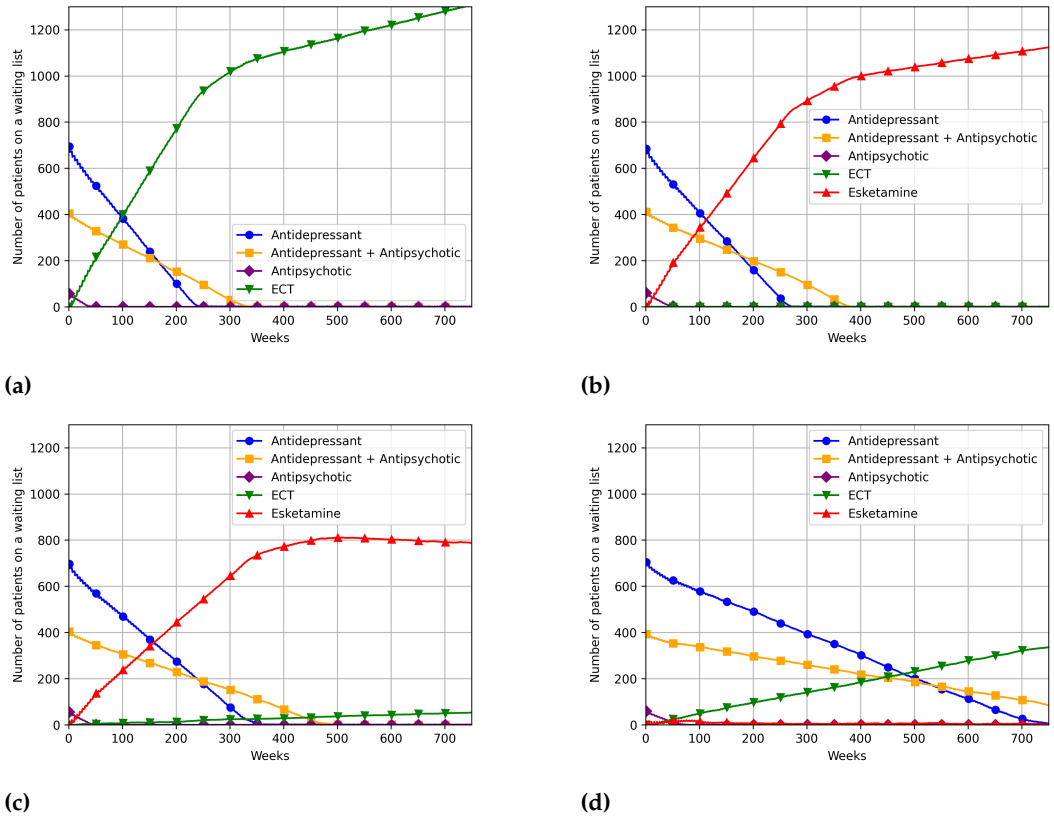


Figure 5. Weekly evolution of the number of patients on the waiting list, depending on the allocated capacity to esketamine, using the Hybrid ABSD model. (a) No esketamine (b) 10% esketamine capacity (c) 20% esketamine (d) 40% esketamine

40% esketamine capacity, the proportion of patients on a waiting list gradually decreases over time, reaching a value of approximately 0.2 at the end of the simulation. At a 20% esketamine capacity, the number of patients waiting initially decreases and then stabilises around a value of 0.4. The pathways with a 10% esketamine capacity and no esketamine initially show a slight decrease but then start to stabilise sooner and at a higher value of approximately 0.6 for the 10% esketamine capacity scenario and 0.7 for the no esketamine scenario. As time progresses, the differences in the proportion of patients waiting between pathways with differing esketamine capacities become larger.

3.3. Cost-effectiveness

The TRD pathway including esketamine treatment was cost-effective across all capacities, providing higher QALYs at only a slightly higher cost. At a base-case esketamine capacity of 20%, the average QALY was 9.42 (CI 9.63 - 9.47), resulting in an incremental QALY of 1.46 compared to the pathway without esketamine. The total cost per patient was € 395,326.5 (CI 395,263.83 - 395,389.16), resulting in an ICER of 1273.01 (CI 1107.76 - 1438.27) for the 20% esketamine pathway compared to the pathway without esketamine. The ICER for each capacity was below the willingness-to-pay (WTP) threshold of €50,000 per QALY gained suggested by Janssen, indicating favourable cost-effectiveness. Additionally, the Net Monetary Benefit (NMB) was positive in all scenarios, suggesting that the monetary value of health benefits exceeded the intervention costs. These findings are detailed in Table 2. The file containing full statistical results, called “aggregated_results.json”, can be found in the associated repository (Kitak & Fron, ABSD 2024).

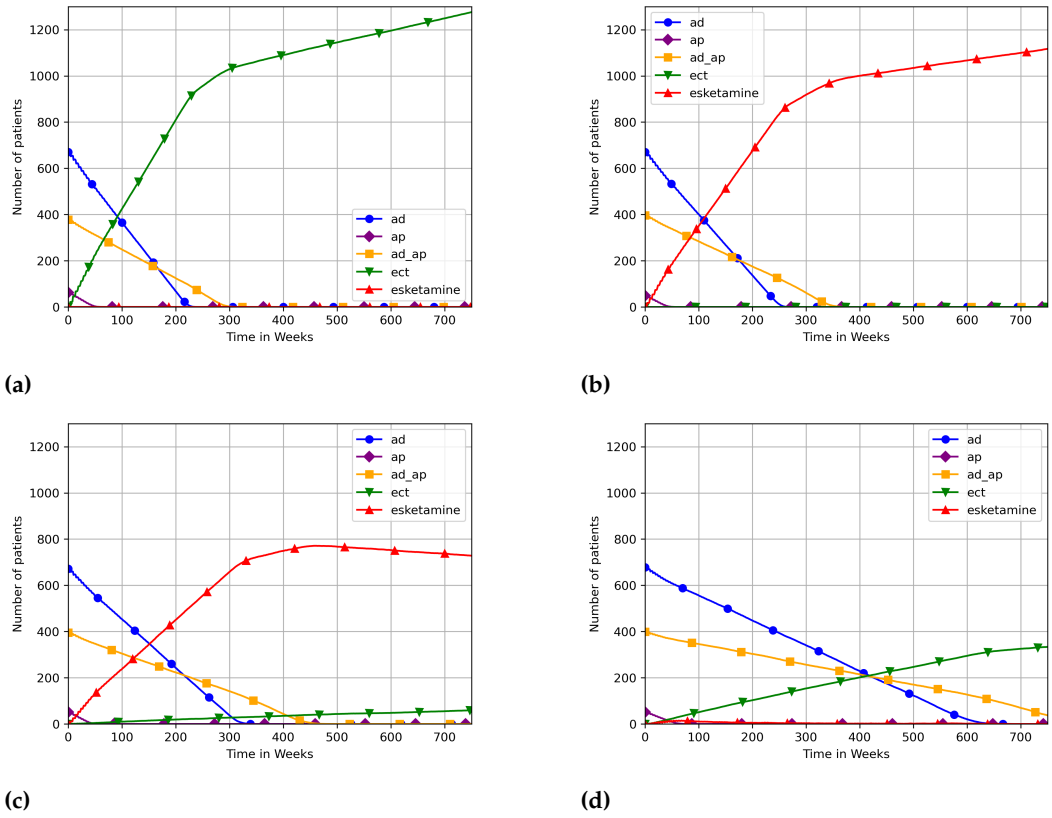


Figure 6. Weekly evolution of the number of patients on the waiting list, depending on the allocated capacity to esketamine using the Unified ABSD model. (a) No esketamine (b) 10% esketamine capacity (c) 20% esketamine (d) 40% esketamine.

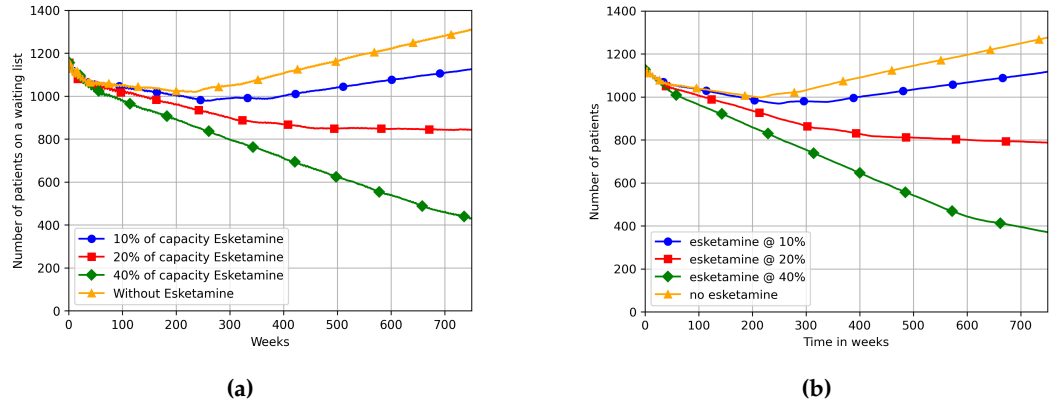


Figure 7. Weekly evolution of the total proportion of the patient population on the waiting list for the (a) Hybrid ABSD and model (b) Unified ABSD model.

Table 2. Relevant costs for cost-effectiveness analysis with varying esketamine capacities; Hybrid ABSD model.

	None	10% Cap.	20% Cap.	40% Cap.
Direct cost/patient	€3,147.1	€4,836.4	€7,811.6	€12,181
Indirect cost/patient	€390,351.9	€389,365.1	€387,514.9	€384,939
Total cost/patient	€393,499	€394,201.5	€395,326.5	€397,120.0
ICER	-	€1,330.04	€1,273.01	€1,401.77
NMB	-	€28,830.94	€70,911.41	€126,516.83
Avg. QALYs	7.96	8.55	9.42	10.56

4. Discussion

Our study delves into the integration of esketamine, a promising candidate drug in clinical trials, into the current depression treatment framework, addressing the critical lack of a standardised treatment pathway for TRD - a gap that contributes to protracted waiting times and spiralling costs. Until now, the real-world implications of esketamine's incorporation in terms of patient outcomes, waiting times, and cost-effectiveness have remained largely unexplored. Our findings reveal that the inclusion of an esketamine treatment step into the depression care pathway, particularly at higher treatment capacities, substantially decreases waiting times and enhances patient outcomes in terms of remission and recovery rates and higher average QALY values compared to the pathway without esketamine. Economically, the esketamine pathway not only proves to be more cost-effective with increased QALYs at only slightly higher total cost per patient than alternatives but also achieved a positive NMB, a key indicator of its overall viability.

Previous research primarily focused on comparing the costs of individual treatment steps, such as esketamine and Electroconvulsive Therapy (ECT). Our study takes a broader perspective by evaluating the impact of an esketamine step on the entire existing treatment pathway. This comprehensive approach captures the cascading effects of treatment interactions and patient flow dynamics, demonstrating esketamine's cost-effectiveness within the full treatment context. Our models provide a more realistic simulation of depression care dynamics, offering robust support for esketamine's economic viability in TRD management.

Furthermore, the trends in waiting times and remission/recovery proportions over time indicate a notable inflection point at approximately 300-500 weeks, depending on the esketamine capacity, which can be attributed to the initial phase where treatment stocks are being saturated. Beyond this period, the models begin to reflect more realistic patient flow and disease progression, which aligns more closely to real-world operational behaviours.

Although real-world waiting list sizes for treatments in the TRD pathway are long and underscore a pressing need for re-evaluation, the escalating waiting list sizes in our models are exaggerated. This can be attributed to the sequential progression of patients through the treatment pathway. Initially, patients commence with the first treatment step, advancing to subsequent steps only if the earlier treatments prove ineffective. However, this linear progression might not fully capture the dynamic nature of real-world patient allocation to treatments. In practice, psychiatrists and healthcare professionals likely consider waiting times as a factor in their decision-making process. For example, if a patient does not respond to an initial antidepressant treatment and the next step in the sequence, esketamine, may have significantly longer waiting times compared to another Untried treatment option, healthcare providers might prefer to refer the patient to the treatment option with shorter waiting times. In this context, the unified ABSD model offers a more nuanced approach to capacity planning, making implementation of complex logic more accessible. On the other hand, Hybrid ABSD, while valuable, has certain limitations not present in Unified ABSD, such as accounting for fluctuating demand patterns or the impact of socioeconomic factors on mental health needs. Integrating the strengths of both models and advancing Unified ABSD could lead to a more robust and effective strategy for managing psychiatric service capacities, ultimately reducing waiting times and improving patient care.

In addition, the comparative study between the Hybrid ABSD and Unified ABSD models presents a nuanced perspective on model validation in the absence of real-world data. Hybrid ABSD's architecture, combining ABM and SD, has a track record of reliability and accuracy, as evidenced by its validation in existing literature. This model's strength lies in its robustness and its suitability for scenarios with quantifiable inputs, such as transition probabilities and stock capacities, which align well with data typically presented as normal distributions. However, the complexity associated with integrating and synchronizing two distinct models presents challenges in design, comprehension, and communication as the model scales up in size. Additionally, there are limited software tools that effectively support the integration of SD and ABM. In contrast, Unified ABSD was designed to

overcome these barriers and create a user-friendly and scalable model, so that future projects have a more powerful platform they can adapt for their own use. Unified ABSD merges elements of ABM and SD into a singular framework, introducing an intriguing flexibility and the ability to incorporate qualitative data, allowing it to tackle more complex systems with intricate transitional logic. This versatility is crucial for simulations that require a more holistic view of the system, going beyond just quantitative measures, thus more valuable in simulating mental healthcare systems. Despite methodological disparities between the models, such as the decision-tree for patient allocation to first-line treatments in the unified ABSD model compared to fixed percentages in the hybrid ABSD model, the consistent results across both models underscore the robustness of our novel modeling approach.

4.1. Limitations

Being the first of its kind, the unified ABSD model acts as a solid proof of concept but remains broadly immature and untested outside of our specific case study. It is imperative to emphasize the need for further scrutiny and validation, especially in the domain of cost-effectiveness analysis. While our study has established the groundwork for the model's efficacy, it's important to note that we did not conduct a comprehensive cost-effectiveness analysis, highlighting a significant area for future development. In general, there is room for refinement in the model's intricacies, and architectural enhancements could yield more precise insights into the intricacies of the depression treatment pipeline.

The reliability and validity of the model's outputs are heavily contingent on the quality and relevance of the input data. In this context, the studies we utilized exhibited a notable degree of heterogeneity in outcome measures. Similarly, the sampled studies were based on demographics other than the Netherlands due to a lack of availability of Dutch studies. The incorporation of Dutch data would undoubtedly enhance the ecological validity of the models. It's worth mentioning that our analysis primarily relied on mean values with high standard deviations, indicating significant variability in the data. This variability suggests that while our findings are informative, they may not fully capture the nuances of individual patient experiences and responses. Furthermore, the absence of highly specific and pertinent real-world evidence for our research objective underscores the limitations of validating the Unified ABSD. Our chosen validation method is robust and reliable within the constraints of this data limitation. Still, it's essential to acknowledge that the absence of real-world data points for comparison leaves us with some uncertainty regarding the model's validation.

4.2. Future research

The findings from our study represent an initial recommendation for the integration of esketamine into the depression treatment pathway for TRD and hold potential implications for future policy adaptations. However, given the inherent limitations and scope of our current study, it is evident that further research is essential to gain a more comprehensive understanding of areas within the Dutch healthcare system that can benefit from improvement.

To estimate the true impact of esketamine on the Dutch healthcare system, it is imperative to utilize data that accurately represents the Dutch population. This approach would enhance the validity of our models significantly. Moreover, substituting estimations with real-life values would further bolster the model's validity. Such a data-driven approach would enable a more detailed and precise assessment of treatment outcomes, patient flow dynamics, and other crucial parameters. Analyzing data at the individual level allows us to identify specific patterns and variations that mean values alone may obscure. In the future, incorporating patient data from real-life observations could serve to enhance the ecological validity of the model.

In addition to these considerations, our study recognizes the importance of evaluating the impact of esketamine on hospitalization rates and associated costs. While our

current models did not encompass hospitalization due to time constraints and modeling complexities, it is a vital factor, especially for patients at risk of suicide and severe side effects. Esketamine, as indicated by numerous clinical trials (e.g., Lally et al., 2014; Larkin et al., 2011; Diazgranados et al., 2010; Price et al., 2009), shows a potential to decrease the risk of suicide and severe symptoms such as anhedonia, suggesting a lower probability of hospitalisation. Furthermore, the likelihood of hospitalisation generally increases with multiple treatment interventions. Esketamine, being an effective treatment with a relatively high remission rate and a relatively low relapse rate, could potentially reduce the need for further treatments and subsequently lower hospitalization costs. Exploring this aspect could provide valuable insights into the overall cost-effectiveness of esketamine, taking into account not only direct treatment costs but also the indirect savings from potentially reduced hospitalization rates.

Moreover, a prospective model could incorporate variables to account for patient mortality due to various reasons, especially for individuals engaging in suicidal behavior, which can impact the overall recovery rate. Moreover, it has been suggested that treatments affect individuals differently per age, gender or ethnicity, which is something we have not explored. As previous studies have indicated remarkable differences across sex for the diagnosis and treatment of MDD (Salk et al., 2017), performing sub-group analyses could provide useful insights and further implications for the treatment. In addition, the Unified ABSD model was built with the capability to do this.

Our novel modelling technique is adaptable for modelling other treatments beyond esketamine, and can potentially be used as a general tool with some slight adjustments. This offers promising avenues to investigate the treatment pipelines of various conditions in the future using the tool we have developed. Additionally, many mental disorders, especially MDD, are comorbid (Read et al., 2017), hence investigating the interaction between treatment pipelines would add an insightful level of complexity.

5. Conclusion

In conclusion, our study represents a step towards addressing the critical gap in standardised treatment pathways for TRD. Our findings show that integrating esketamine as an additional step in the current depression care pathway leads to notable improvements in patient outcomes, reduced waiting times, and enhanced cost-effectiveness, suggesting that esketamine is a promising candidate for TRD treatment. While our models show consistent results, validating our novel Unified ABSD model, it serves as a proof of concept and future research should focus on refining the model's architecture, incorporating more representative data, and exploring the interaction between treatment pipelines for co morbid mental disorders. These advancements hold promise for shaping future policy decisions and optimising mental health care strategies.

Author Contributions: **Calin Alecu**: Cover letter, abstract, introduction, cost data gathering, final editing. **Julia Bertsch**: Conceptualized and developed the new Unified ABSD model, designed its architecture, implemented it for our research, wrote the methodology section of the paper related to the new model as well as the treatment pathway and underlying model section, developed the relapse function, performed the capacity estimations, and assisted the data collection team. Facilitated the transition of the paper from Word to LaTeX, final editing. **Madalina Fron**: Implementation of Hybrid ABSD model. Organisational tasks: coach meetings, weekly planning. Writing contribution: ABSD results, model comparison and validation, related case studies on hybrid modelling usage in healthcare, connecting AB and SD models. **Ellen Heck**: Writing contributions included: the data collection part of the methodology, discussion, conclusions and rebuttal. Responsible for the reference list and checking our citations. Contributed to the systematic review of papers, by gathering data and summarising findings. Scheduled our weekly supervisor meetings. **Tom Kitak**: Implementation of Hybrid ABSD model, alignment between models, writing contribution: part of underlying model architecture, result figures and data, Hybrid ABSD architecture diagram and implementation description. **Marcello Pepe**: Conceptualization of models, data gathering, writing:

data analysis, results, discussion. **Joey van Zanten**: Significant portion of the data gathering, with a particular focus on the clinical aspects. Assisted with the conceptual development of Unified ABSD model. Contributed to the writing of the data collection, discussion and conclusion.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Code and Data Availability Statement: Data supporting the findings of this research can be accessed via GitHub, with further details or additional data available upon direct communication with the authors. The code for the Hybrid ABSD model is available at https://github.com/tomkitak/system-dynamics-and-agent-based-modeling, while the code for the Unified ABSD can be found at https://github.com/AnotherJulia/Atlas4TRD. Researchers interested in gaining further insights or exploring collaborative opportunities are encouraged to contact the authors

Acknowledgments: The authors deeply thank Brian Analikwu, Agathe Henocq, Dr. Anderson Mora Cortes, Dr. Jeroen van Rooij for their advice on experimental design and writing. Additional appreciation is devoted to the course coordinators Dr. Hegias Mira Bontenbal, Dr. Johanna Colgrove and their team.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A Model Parameter Specifications

Table A1. Capacity details for each treatment in best, base, and worst-case scenarios.

Treatment	Best Case	Base Case	Worst Case
Antidepressants (AD)	10	15	15
Antipsychotics (AP)	5	10	15
AD + AP	10	10	10
ECT	5	5	5
Esketamine	20	10	5

Table A2. Cost details, patient flow, and initial number of patients.

Parameter	AD	AP	AD+AP	ECT	Esketamine
Treatment Phase Cost/month	€924	€923	€927	€5200	€3045
Maintenance Phase Cost/month	€135	€133	€138	€135	€1320
Average Wages of Dutch Population/week	€1214				
Number of Initial Patients	1156				
Patient Flow per Week	1				

Table A3. Clinical data: Relapse, Remission, Response rates, and Treatment Duration.

Parameter	AD	AP	AD+AP	ECT	Esketamine
Relapse Rate	0.6 after 6 months	0.125 after 3 months	0.2 after 8 months	0.5 after 6 months	0.267 after 6 months
Remission Rate (after 4 weeks)	0.34	0.2978	0.3886	0.591	0.472
Response Rate (after 4 weeks)	0.402	0.507	0.524	0.414	0.784
Treatment Duration	4 weeks/28 days				

Appendix B Architecture Diagram

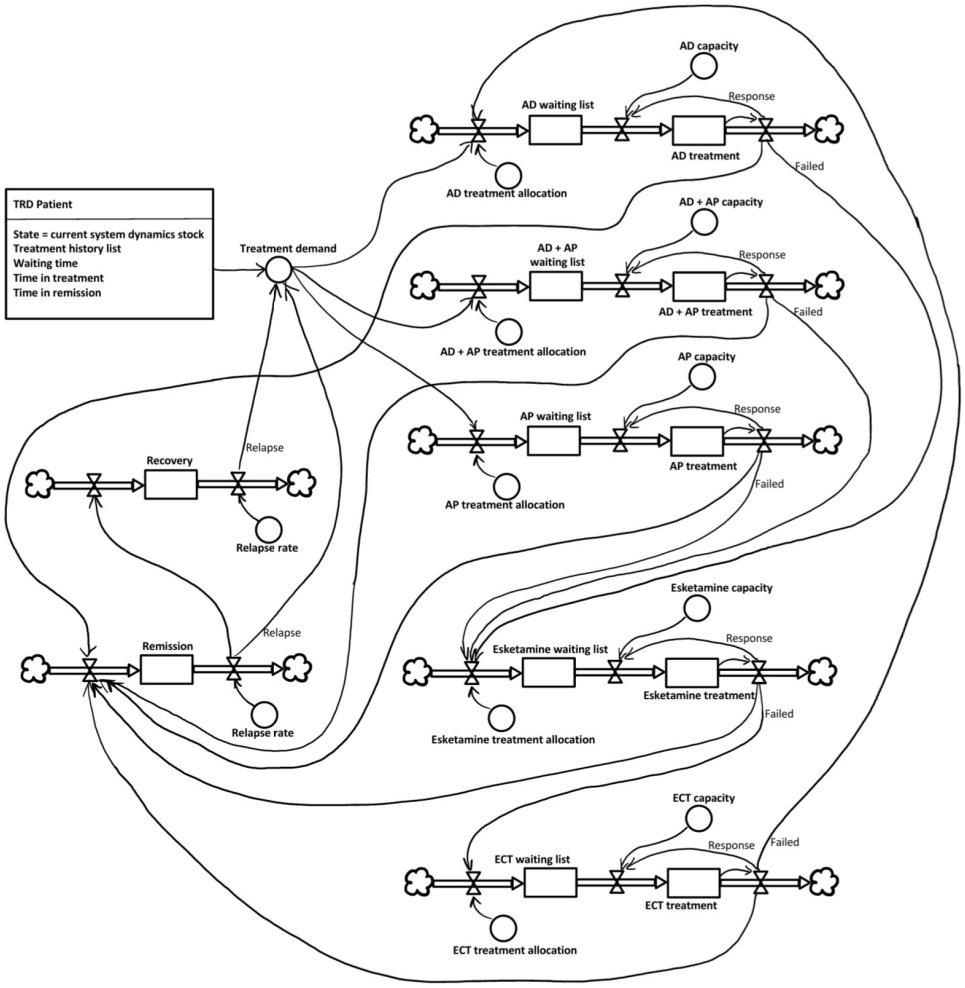


Figure A1. Hybrid Agent Based System Dynamics Model with Esketamine as part of treatment pathway

Note. The box in the top left represents TRD patient agents from ABM. The rest is SD diagram, where rectangles are stocks, circles are converters, thick arrows are flows, and thin arrows are connectors.

References

1. Nolen-Hoeksema, S. *Abnormal Psychology*, 8 ed.; McGraw-Hill Education, 2019.
2. Baxter, A.J.; Page, A.; Whiteford, H.A. Factors Influencing Risk of Premature mortality in Community Cases of Depression: A Meta-Analytic Review. *Epidemiology Research International* **2011**, *2011*, 1–12. https://doi.org/10.1155/2011/832945.
3. de Graaf, R.; ten Have, M.; van Dorsselaer, S. *De Psychische Gezondheid van de Nederlandse Bevolking: NEMESIS-2: Opzet en Eerste Resultaten*; Trimbos-instituut: Utrecht, 2010.
4. Nuijen, J.; van Bon-Martens, M.; de Graaf, R.; ten Have, M.; van der Poel, A.; de Beurs, D.; Nielen, M.; Verhaak, P.; Voorrips, L. View of Depression: The Condition, Prevention, and Care, 2018.
5. Al-Harbi, K.S. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Preference and Adherence* **2012**, *6*, 369–388. https://doi.org/10.2147/PPA.S29716.
6. Heerlein, K.; Perugi, G.; Otte, C.; Frodl, T.; Degraeve, G.; Hagedoorn, W.; Oliveira-Maia, A.J.; Perez Sola, V.; Rathod, S.; Rosso, G.; et al. Real-world evidence from a European cohort study of patients with treatment resistant depression: Treatment patterns and clinical outcomes. *Journal of affective disorders* **2021**, *290*, 334–344. https://doi.org/10.1016/j.jad.2021.03.073.
7. Jain, S.; Gupta, S.; Li, V.W.; Suthoff, E.; Arnaud, A. Humanistic and economic burden associated with depression in the United States: a cross-sectional survey analysis. *BMC Psychiatry* **2022**, *22*. https://doi.org/10.1186/s12888-022-04165-x.
8. Bosmans, J.E.; De Bruijne, M.C.; De Boer, M.R.; Van Hout, H.P.J.; Van Steenwijk, P.C.; Van Tulder, M.W. Health care costs of depression in primary care patients in The Netherlands. *Family Practice* **2010**, *27*, 542–548. https://doi.org/10.1093/fampra/cmq033.
9. Lepine, B.A.; Moreno, R.A.; Campos, R.N.; Couttolenc, B.F. Treatment-Resistant depression increases health costs and resource utilization. *Revista Brasileira de Psiquiatria* **2012**, *34*, 379–388. https://doi.org/10.1016/j.rbp.2012.05.009.
10. Mahase, E. Esketamine is approved in Europe for treating resistant major depressive disorder. *The BMJ* **2019**, p. l7069. https://doi.org/10.1136/bmj.l7069.
11. Brice, S.N.; Harper, P.R.; Gartner, D.; Behrens, D.A. Modeling disease progression and treatment pathways for depression jointly using agent based modeling and System Dynamics. *Frontiers in Public Health* **2023**, *10*. https://doi.org/10.3389/fpubh.2022.1011104.
12. American Psychiatric Association, DSM-5 Task Force. *Depressive Disorders*, 5th ed.; American Psychiatric Publishing, Inc., 2013. https://doi.org/10.1176/appi.books.9780890425596.
13. Bertsch, J. Atlas4TRD Version (1.0.0), n.d. Retrieved January 29, 2024.
14. Bradhurst, R.A.; Roche, S.E.; East, I.J.; Kwan, P.; Garner, M.G. A hybrid modelling approach to simulating foot-and-mouth disease outbreaks in Australian livestock. *Frontiers in Environmental Science* **2015**, *3*. https://doi.org/10.3389/fenvs.2015.00017.
15. Bukh, J.D.; Bock, C.; Vinberg, M.; Kessing, L.V. The effect of prolonged duration of untreated depression on antidepressant treatment outcome. *Journal of Affective Disorders* **2013**, *145*, 42–48. https://doi.org/10.1016/j.jad.2012.07.008.
16. Macro Economic Outlook (MEV) 2023, 2023.
17. Duffy, L.; Clarke, C.S.; Lewis, G.; Marston, L.; Freemantle, N.; Gilbody, S.; Hunter, R.; Kendrick, T.; Keßler, D.; King, M.; et al. Antidepressant medication to prevent depression relapse in primary care: the ANTLER RCT. *Health Technology Assessment* **2021**, *25*, 1–62. https://doi.org/10.3310/hta25690.
18. Diazgranados, N.; Ibrahim, L.; Brutsché, N.E.; Ameli, R.; Henter, I.D.; Luckenbaugh, D.A.; Machado-Vieira, R.; Zarate, C.A. Rapid resolution of suicidal ideation after a single infusion of an N-Methyl-D-Aspartate antagonist in patients with Treatment-Resistant major Depressive Disorder. *The Journal of Clinical Psychiatry* **2010**, *71*, 1605–1611. https://doi.org/10.4088/jcp.09m05327blu.
19. Gillain, B.; Degraeve, G.; et al. Real-World Treatment Patterns, Outcomes, Resource Utilization and Costs in Treatment-Resistant Major Depressive Disorder: PATTERN, a Retrospective Cohort Study in Belgium. *PharmacoEconomics - open* **2022**, *6*, 293–302. https://doi.org/10.1007/s41669-021-00306-2.
20. Haase, D.; Haase, A.; Kabisch, N.; Kabisch, S.; Rink, D. Actors and factors in land-use simulation: the challenge of urban shrinkage. *Environmental Modelling & Software* **2012**, *35*, 92–103. https://doi.org/10.1016/j.envsoft.2012.02.012.
21. Kitak, T.; Fron, M.O. ABSD Version (1.0.0), n.d. Retrieved January 29, 2024.
22. Lally, N.; Nugent, A.C.; Luckenbaugh, D.A.; Ameli, R.; Roiser, J.P.; Zarate, C.A. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Translational Psychiatry* **2014**, *4*, e469. https://doi.org/10.1038/tp.2014.105.
23. Larkin, G.L.; Beautrais, A.L.; Turelli, R.; Sanacora, G.; Powsner, S.M.; Lippmann, M.J.; Krystal, J.H. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *European Psychiatry* **2011**, *26*, 1607. https://doi.org/10.1016/s0924-9338(11)73311-9.
24. McCrone, P.; Rost, F.; Koeser, L.; Koutoufa, I.; Stephanou, S.; Knapp, M.; Goldberg, D.; Taylor, D.; Fonagy, P. The economic cost of treatment-resistant depression in patients referred to a specialist service. *Journal of Mental Health* **2017**, *27*, 567–573. https://doi.org/10.1080/09638237.2017.1417562.
25. Memon, R.I.; Sattar, N.; Faquih, A.E.; Fida, A.; Abbas, N.; Chaudhary, A.M.D.; Qayyum, Z. Effectiveness and Safety of Ketamine for Unipolar Depression: a Systematic Review. *Psychiatric Quarterly* **2020**, *91*, 1147–1192. https://doi.org/10.1007/s11126-020-09830-6.
26. Monteggia, L.M.; Zarate, C.A. Antidepressant actions of ketamine: from molecular mechanisms to clinical practice. *Current Opinion in Neurobiology* **2015**, *30*, 139–143. https://doi.org/10.1016/j.conb.2014.12.004.

27. Montgomery, S.; Åsberg, M. A New Depression Scale Designed to be Sensitive to Change. *The British Journal of Psychiatry* **1979**, *134*, 382–389. https://doi.org/10.1192/bjp.134.4.382.
28. Mrazek, D.A.; Hornberger, J.; Altar, C.A.; Degtiar, I. A review of the clinical, economic, and societal burden of Treatment-Resistant Depression: 1996–2013. *Psychiatric Services* **2014**, *65*, 977–987. https://doi.org/10.1176/appi.ps.201300059.
29. Benefits outside the Netherlands for people who are unable to work due to sickness or disability. https://www.netherlandsworldwide.nl/about-netherlands-worldwide, 2024.
30. Ouda, E.; Sleptchenko, A.; Simsekler, M.C. Comprehensive review and future research agenda on discrete-event simulation and agent-based simulation of emergency departments. *Simulation Modelling Practice and Theory* **2023**, *129*, 102823. https://doi.org/10.1016/j.simpat.2023.102823.
31. Peeters, F.; Ruhé, H.G.; Wichers, M.; Abidi, L.; Kaub, K.; Lande, H.; Spijker, J.; Huibers, M.J.; Schene, A.H. The Dutch Measure for quantification of Treatment Resistance in Depression (DM-TRD): an extension of the Maudsley Staging Method. *Journal of Affective Disorders* **2016**, *205*, 365–371. https://doi.org/10.1016/j.jad.2016.08.019.
32. Price, R.B.; Nock, M.K.; Charney, D.S.; Mathew, S.J. Effects of intravenous ketamine on explicit and implicit measures of suicidality in Treatment-Resistant Depression. *Biological Psychiatry* **2009**, *66*, 522–526. https://doi.org/10.1016/j.biopsych.2009.04.029.
33. System dynamics and agent based modeling in Python. https://bptk.transentis.com/.
34. Quilty, L.C.; Robinson, J.; Rolland, J.; De Fruyt, F.; Rouillon, F.; Bagby, R.M. The structure of the Montgomery–Åsberg depression rating scale over the course of treatment for depression. *International Journal of Methods in Psychiatric Research* **2013**, *22*, 175–184. https://doi.org/10.1002/mpr.1388.
35. Read, J.R.; Sharpe, L.; Modini, M.; Dear, B.F. Multimorbidity and depression: A systematic review and meta-analysis. *Journal of Affective Disorders* **2017**, *221*, 36–46. https://doi.org/10.1016/j.jad.2017.06.009.
36. Schurer, M.; Matthijsse, S.M.; Vossen, C.Y.; van Keep, M.; Horscroft, J.; Chapman, A.M.; Akehurst, R.L. Varying Willingness to Pay Based on Severity of Illness: Impact on Health Technology Assessment Outcomes of Inpatient and Outpatient Drug Therapies in The Netherlands. *Value in Health* **2022**, *25*, 91–103. https://doi.org/10.1016/j.jval.2021.08.003.
37. Stapelberg, N.J.; Smoll, N.R.; Randall, M.; Palipana, D.; Bui, B.; Macartney, K.; Khandaker, G.; Wattiaux, A. A discrete-event, simulated social agent-based network transmission (dessabnet) model for communicable diseases: Method and validation using SARS-COV-2 data in three large Australian cities. *PLOS ONE* **2021**, *16*. https://doi.org/10.1371/journal.pone.0251737.
38. Sullivan, P.W.; Ghushchyan, V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Medical Decision Making* **2006**, *26*, 410–420. https://doi.org/10.1177/0272989X06290495.
39. Spijker, J.; Bockting, C.L.H.; Meeuwissen, J.A.C.; van Vliet, I.M.; Emmelkamp, P.M.G.; Hermens, M.L.M.; Van Balkom, A.L.J.M. Multidisciplinaire richtlijn depressie (tweede revisie). Trimbos-instituut, 2011.
40. Swinerd, G.G.; McNaught, A.D. Linking Agent-Based and System Dynamics Models of Complex Systems. *System Dynamics Review* **2012**, *28*, 138–155.
41. van den Belt, M. *Mediated Modeling: A System Dynamics Approach To Environmental Consensus Building*; Island Press, 2004.
42. Young, A.H.; Cubała, W.J.; Nielsen, R.E.; Popova, A.; Ito, T.; Mulhern-Haughey, S.; Pirotte, N.; Rive, B.; Thilakarathne, P.; Usankova, I.; et al. Esketamine Nasal Spray Improves Rate and Time to Remission Versus Quetiapine Extended Release in Subgroups of Patients With Treatment Resistant Depression and Two or Three Plus Prior Treatment Failures: Results From ESCAPE-TRD, a Randomised Phase IIIb Trial. *BJPsych Open* **2023**, *9*, S75. https://doi.org/10.1192/bjo.2023.245.
43. Medication costs. https://www.medicijnkosten.nl/.