Using Machine Learning and Real-World Data to Identify Patients with Early Stage Bipolar-I Disorder for whom Aripiprazole Monohydrate LAIs are Likely to be a Favorable Treatment Option

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Background

Aripiprazole monohydrate two-month ready-to-use (Ari 2MRTU) and aripiprazole monohydrate once-monthly (AOM) are long-acting injectable antipsychotics approved in the United States for the maintenance monotherapy treatment of bipolar-I disorder (BP-I) in adults.[1,2] Real-word evidence exists to support the early initiation of long-acting injectable antipsychotics, showing improved clinical outcomes for patients diagnosed with BP-I[3]

In an open-label, multiple-dose, randomized parallel-arm, multicenter trial, Ari 2MRTU provided therapeutic plasma levels of aripiprazole, with an efficacy profile comparable to AOM for at least two months after a single dose,[4] yet there is no real-world data to inform selection for the two formulations

Insight into demographic, clinical (e.g., comorbidities or medical history), specific treatment choice and timing factors that inform most favorable response to Ari 2MRTU and AOM in patients diagnosed with BP-I may support clinicians in making personalized treatment decisions. Prior machine learning (ML) models utilizing AOM clinical trial datasets were able to identify baseline factors predicting response to AOM in patients diagnosed with BP-I

Study objectives:

Develop and validate machine learning models to predict optimal treatment response to Ari 2MRTU and AOM in early-stage patients diagnosed with BP-I

Identify and characterize key predictive factors, including demographic, clinical (e.g., medical history, comorbidities), specific treatment choice and/or timing, associated with favorable treatment outcomes for Ari 2MRTU and AOM in BP-I

Methods

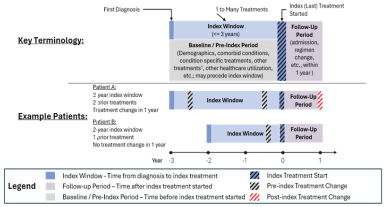
Data Source and Sample Selection

- This exploratory study utilized real-world data from a large, integrated electronic medical record (EMR) and an open claims database in the Atropos Evidence Network™ covering all sites of care and pharmacy fills for US patients from 2022 to 2025
  - Using ICD-10 codes for BP-I diagnosis, the potential pool of patients was N=17,674,042
  - Across the datasets, hundreds of potential features were evaluated and eventually 271 features were selected
  - Examples of potential features originating from EMR included were age, gender, PHQ9 and GAD7 scores
- Adult patients (≥18 years) were included in the model sample if they (**Figure 1**):
  - Were within 3 years of initial diagnosis of BP-I, initiated any listed antipsychotic treatment
  - Had an index treatment, defined as the last treatment initiated within 3 years of initial diagnosis, was on or after Jan. 2022
  - Had at least 1 year of follow-up data from the index treatment date

Exploratory Machine Learning Approach

- The primary machine learning exploratory approach used targeted minimum loss-based super learning ensembles to incorporate drivers of observed treatment selection and likely outcomes in predicting characteristics of patients diagnosed with BP-I for whom Ari 2MRTU and AOM are likely to be favorable treatment options
- A four-task machine learning framework was applied across 9 intervention categories, beginning with treatment propensity modeling (task 1) and outcome prediction (task 2), followed by optimal individual treatment rule learning (task 3) and finally extending to optimal treatment policy learning for identified groups of patients (task 4) (**Figure 2**)
- Primary treatment success measures were absence of (1) all cause inpatient admission and (2) antipsychotic treatment regimen change during the 12-month post index treatment period
- Model training across all machine learning tasks was conducted on the same randomly selected 70% of the patient sample. Estimates of predictive utility and benefits of implementing the learned policy were based on the 30% validation sample

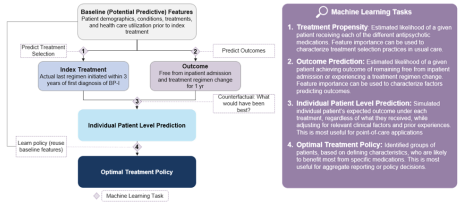
Figure 1: Key terminology



Results

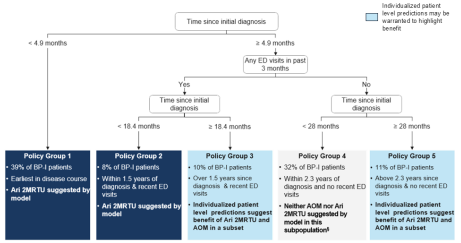
- Key steps in the predictive modelling process are shown in **Figure 2**:
  - Modeling for tasks 1 and 2 predict treatment selection and outcomes based on how patients **were treated** in the data, while modeling for tasks 3 and 4 base predictions on how this model predicts patients **would optimally** be treated
- Overall, there were 98,972 patients who started antipsychotic treatment within 3 years of initial BP-I diagnosis who had over 1 year of follow-up data. The most common index treatment was an oral atypical antipsychotic. There were 183 and 2,917 patients with Ari 2MRTU and AOM as an index treatment, respectively (**Table 1**)
- The optimal treatment policy model output suggested Ari 2MRTU as the optimal treatment choice for nearly half of patients diagnosed with BP-I in this sample (**Figure 3**)
- Ari 2MRTU is suggested to be optimal treatment choice compared to other options for patients within 5 months of diagnosis and those within 18 months with prior emergency department visits (**Figure 3**)
- AOM showed benefits for some patients within this model in policy groups 3 and 5, but is not suggested above Ari 2MRTU (**Figure 3**)
- The ranking of predictive features that impact treatment propensity and outcome prediction modelling are shown in **Table 2**
- Overall, the optimal treatment policy model suggested that Ari 2MRTU should be used more frequently and earlier in the disease course for patients with BP-I
- ML-recommended usage suggests very limited use of oral treatments to improve outcomes of early-stage patients (**Table 3**)

Figure 2: Four key tasks in the machine learning approach



Abbreviations: BP-I – Bipolar-I disorder
Note: Number and type of prior treatment regimens were excluded as a feature from treatment propensity task since it reduced interpretability

Figure 3: Optimal treatment policy suggested by machine learning model



- **Ari 2MRTU was suggested by model as optimal treatment for nearly half of patients with BP-I (policy groups 1 and 2)**
- **In policy groups 3 and 5, the policy suggested no clear treatment, which implies that individual patient level prediction should be applied as some patients benefit from Ari 2MRTU and AOM**

Abbreviations: BP-I – Bipolar-I disorder, AOM – Aripiprazole once-monthly, Ari 2MRTU – Aripiprazole 2-month ready-to-use, ED – Emergency Department
§ ML models are not intended to dictate clinical actions or replace professional judgment, but to assist clinicians in decision-making. many patients in policy group 4 would have improved outcome on AOM or AriM RTU compared to the treatment they received

Table 1: Patient demographics in overall BP-I sample

	Total	Oral Antipsychotics	AOM	Ari 2MRTU	Other LAI
N	98,972	88,206	2,917	183	7,666
Mean Age (SD)	41.12 (15.29)	41.43 (14.41)	37.00 (13.39)	37.38 (13.04)	39.22 (14.24)
Male sex	38.4%	37.4%	41.5%	35.0%	50.0%
Race/Ethnicity					
Asian	0.4%	0.4%	0.5%	0.5%	0.4%
Black	1.3%	1.3%	1.7%	0.0%	1.9%
White	20.0%	20.7%	15.2%	21.3%	13.8%
Unknown	78.3%	77.7%	82.5%	78.1%	84.0%
Hispanic or Latino	2.3%	2.3%	2.1%	2.7%	2.0%
Not Hispanic or Latino	51.9%	52.6%	47.1%	45.9%	45.0%
Unknown	45.9%	45.1%	50.8%	51.4%	53.0%

Abbreviations: AOM – Aripiprazole once-monthly, Ari 2MRTU – Aripiprazole two-month ready-to-use, LAI – Long-Acting Injectable, SD – standard deviation

Table 2: Ranking of predictive features impacting index treatment and treatment outcome prediction (top 5)

Index Treatment Model (Task 1)*

Predictive Featured	Gain
Schizoaffective diagnosis (past 12 mos)	0.449
Anticholinergic use (past 12 mos)	0.091
Valproic acid use (past 12 mos)	0.084
Anticholinergic use (past 6 mos)	0.071
Years since initial Dx	0.053

Treatment Outcome Model (Task 2)

Predictive Feature	Gain
Inpatient visit (past 6 mos)	0.350
Inpatient visit (past 12 mos)	0.330
Inpatient visit (past 3 mos)	0.138
ED visits (past 3 mos)	0.117
Schizoaffective diagnosis (past 12 mos)	0.029

- **Schizoaffective diagnosis and history of anticholinergic products use drive most of the index treatment prediction**
- **Inpatient visit history is the strongest predictor for treatment outcome of remaining free from inpatient admission and treatment regimen change in 1 year in the follow-up period**

Abbreviations: ED – Emergency department, Dx – Diagnosis
* Excludes number of prior treatments

Table 3: Actual and ML-proposed usage policy patterns for early-stage BP-I treatment

	Actual vs. ML-Proposed Treatment Usage Patterns		
Treatment Regimen	**Usage Pattern in Actual Data**	**Proposed Usage Pattern per Policy**	**Individualized Patient Level Predictions**
Oral treatments#	89.1%	10.7%‡	Estimate of treatment success difference was +10% in favor of LAIs
Long-acting injectables (LAIs)	10.9%	89.3%	

- **Oral antipsychotics were recommended at substantially lower rates by the optimal treatment policy compared with real-world use**
- **ML policy points to shift to earlier initiation of LAIs in place of current oral antipsychotics for positive treatment outcomes in patients with early-stage BP-I**

Includes typical & atypical antipsychotics
‡ Individualized patient level predictions suggested oral treatments in additional patients based on predictors

Limitations

- The relatively recent FDA approval of Ari 2MRTU (April 2023), combined with requiring at least 1 year of follow-up data in this study limited the number of patients on Ari 2MRTU
- Despite the relatively small number of Ari 2MRTU patients in the data sample (N=183), the sample size is meaningful, producing statistically significant results that are expected to be strengthened as more treatment data becomes available
- Treatment outcomes in the model would be better evaluated through specific disease-specific scales (e.g., Young Mania Rating Scale [YMRS], Clinical Global Impressions-Bipolar Scale [CGI-BP-S]), however this information is not readily available in real-world databases and hence, the team decided to use proxy measures found in other studies, notably Wu et al[5]
- The impact of the study's algorithm has not been assessed at the site level, which is often needed for validation prior to broader use

Conclusions

- An exploratory ML method was used to identify patients within the first 3 years of initial BP-I diagnosis who are optimal responders to Ari 2MRTU and AOM; the model was also able to differentiate between each of these treatment options
- An exploratory ML approach that utilizes real-world data from EMR and open claims may inform optimal treatment selection at the individual and group levels for patients with early-stage BP-I
- Initial findings suggest that patients diagnosed with BP-I may likely benefit from Ari 2MRTU initiation earlier in the disease course; the optimal treatment policy model proposed much lower usage of all oral antipsychotics for early-stage BP-I patients compared to current usage pattern
- This exploratory model has potential for further development through real-world studies at treatment sites to support point-of-care patient treatment and policy decisions. The findings are not intended to dictate clinical actions or replace professional judgment

References

1. Otsuka America Pharmaceutical, Inc. Abilify Asimtufii (aripiprazole) Prescribing information. March 2025
2. Otsuka America Pharmaceutical, Inc. Abilify Maintena (aripiprazole) Prescribing information. March 2025
3. Vieta et al. Bipolar Disorders. 2024; 27(1):7–16
4. McIntyre et al., Current Medical Research and Opinion. 2023; 39(7), 1021–1030
5. Wu et al. JAMA Network Open. 2020; 3(2)

Disclosures

VM is full-time employee of Atropos Health, which received support from Otsuka Pharmaceuticals and Lundbeck for this work. **JJ** and **RL** were employees of Atropos Health, when this work was conducted

BR, **TY**, and **BA** are full-time employees of Guidehouse, which received support from Otsuka Pharmaceuticals and Lundbeck for this work. **IK-K** was a full-time employee of Guidehouse, when this work was conducted

NA and **SN** are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA. **KSBL** was an employee of Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA, when this work was conducted

KH is full time employee of H. Lundbeck A/S, Valby, Denmark and **AMHW** is full-time employee of Lundbeck, LLC, Deerfield, IL, USA

MT received honoraria or consultation fees from Abbott, AbbVie, Alkermes, AstraZeneca, Elan, Gedeon Richter, Intracellular Therapies, Johnson & Johnson, Lilly, Lundbeck, Merck, Minerva, Neurocrine Biosciences, Otsuka, Pfizer, Roche, Sunovion, and Teva. MT was an employee at Lilly (1997–2008); his spouse was an employee at Lilly (1998–2013)

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