Using Machine Learning and Real-World Data to Identify Patients with Schizophrenia 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 treatment of schizophrenia in adults.[1,2] Evidence supports that long-acting injectable (LAI) formulations of antipsychotics are associated with improved clinical outcomes for patients diagnosed with schizophrenia[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

Understanding the demographics, 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 schizophrenia may support clinicians in making personalized treatment decisions

In prior studies, machine learning showed clinical utility for predicting response to antipsychotics in patients diagnosed with schizophrenia.[5,6] Previous machine learning models utilizing AOM clinical trial datasets were able to identify baseline factors predicting response to AOM in patients diagnosed with schizophrenia

Study objectives:

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

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 schizophrenia

Methods

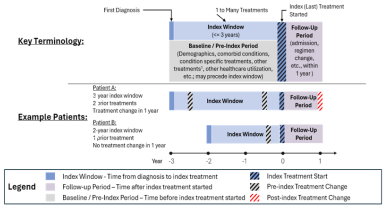
Data Source and Sample Selection

- 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 (F20 with all subtypes) for schizophrenia, the potential pool of patients was N=5,106,297
  - 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 schizophrenia, 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 schizophrenia 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

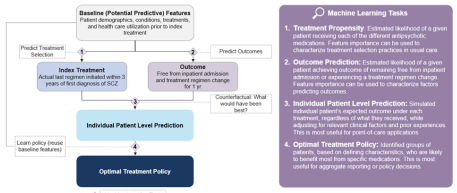
Figure 1: Key terminology



Results

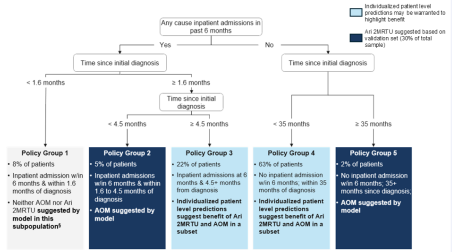
- Key steps in the predictive modelling process are shown in **Figure 2**:
  - Modeling for tasks 1 and 2 predict treatment selection and outcomes based on how patients **were treated** in the data, while modeling for tasks 3 and 4 base predictions on how this model predicts patients **would optimally** be treated
- Overall, there were 97,215 patients who started antipsychotic treatment within 3 years of initial schizophrenia diagnosis who had over 1 year of follow-up data. The most common index treatment was an oral atypical antipsychotic. There were 263 and 3,799 patients with Ari 2MRTU and AOM as an index treatment, respectively (**Table 1**)
- In recently diagnosed patients (over ~2 months) with history of inpatient admissions in the prior 6 months, AOM was suggested as optimal treatment by the machine learning model (**Figure 3**)
- Ari 2MRTU and AOM were the optimal treatment in a subset of patients when utilizing individualized patient level predictions within two policy groups (**Figure 3**)
- **Table 2** indicates predictive features of note, including concurrent medications and inpatient visits at different time frames
- Results between the training and validation sample were inconsistent, as there was a propensity for the estimated benefit of Ari 2MRTU to be higher in validation data set in policy groups where AOM was suggested in the training set
- 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: SCZ – Schizophrenia
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



- AOM is suggested for: Patients with (1) prior inpatient admission history, between 2 and 5 months from diagnosis and (2) over 35 months from SCZ diagnosis
- In policy groups 3 and 4, 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: AOM – Aripiprazole once-monthly, Ari 2MRTU – Aripiprazole 2-month ready-to-use, ED – Emergency Department, SCZ – Schizophrenia
§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 Ari2M RTU compared to the treatment they received

Table 1: Patient demographics in overall SCZ sample

	Total	Oral Antipsychotics	AOM	Ari 2MRTU	Other LAI
N	97,215	77,126	3,799	263	16,027
Mean Age (SD)	42.82 (15.76)	43.76 (15.99)	38.30 (13.83)	39.35 (13.09)	39.41 (14.38)
Male sex	57.2%	56.1%	56.1%	51.7%	63.0%
Race/Ethnicity					
Asian	0.4%	0.4%	0.5%	0.0%	0.3%
Black	2.1%	2.1%	1.9%	1.5%	2.0%
White	10.8%	11.1%	10.6%	13.3%	9.7%
Unknown	86.7%	86.4%	87.0%	85.2%	88.0%
Hispanic or Latino	2.1%	2.2%	2.2%	0.8%	1.8%
Not Hispanic or Latino	38.2%	38.9%	36.9%	38.4%	35.0%
Unknown	59.7%	58.9%	60.9%	60.8%	63.2%

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
Anticholinergic use (past 3 mos)	0.183
Mood stabilizers (past 12 mos)	0.173
Anticholinergic use (past 12 mos)	0.119
Age	0.111
SSRI use (past 12 mos)	0.090

Treatment Outcome Model (Task 2)

Predictive Feature	Gain
Inpatient visit (past 6 mos)	0.434
Inpatient visit (past 12 mos)	0.272
Inpatient visit (past 3 mos)	0.216
ED visits (past 3 mos)	0.055
History of congestive heart failure	0.005

- Anticholinergic use, use of mood stabilizers and age constitute top drivers of predictive index treatment
- Inpatient visit history and emergency department utilization dominates as the strongest predictors 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, SSRI – Selective Serotonin Reuptake Inhibitor
* Excludes number of prior treatments

Table 3: Actual and ML-proposed usage policy patterns for early-stage schizophrenia 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[#]	79.3%	0.0%[‡]	Estimate of treatment success difference was +10% in favor of LAIs
Long-acting injectables (LAIs)	20.7%	100.0%	

- Oral antipsychotics were recommended at much 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 outcome in patients with schizophrenia

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=263), the sample size is meaningful, producing statistically significant results that are expected to be strengthened as more treatment data becomes available
- Complexity in treatment pathways for schizophrenia patients including challenges with adherence and disruptions in care, contributes to the variability in assessing outcomes and inconsistency identified in the ML treatment recommendations
- Treatment outcomes in the model would be better evaluated through specific disease-specific scales (e.g., Positive and Negative Syndrome Scale [PANSS], Clinical Global Impressions-Schizophrenia [CGI-SCH]), 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. The findings are not intended to dictate clinical actions or replace professional judgment

Conclusions

- An exploratory ML method was used to identify patients within the first 3 years of initial schizophrenia diagnosis who are optimal responders to Ari 2MRTU and AOM; the model was also able to differentiate between each 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 at group levels for patients with early-stage schizophrenia
- Machine learning policy provides evidence aligned to expert clinical opinions on use of long-acting injectables, such as Ari 2MRTU and AOM, in early-stage schizophrenia.[7] Specifically, the policy recommended much lower usage of oral antipsychotics for early-stage schizophrenia patients compared to current usage pattern
- Further validation of the exploratory model should be performed, potentially at a treatment site, as more antipsychotic treatment data becomes available, specifically for Ari 2MRTU

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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

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