Title: Safer Use of Antipsychotics in Youth (SUAY)

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Analysis plan for Safety Use of Antipsychotics in Youth (SUAY)

Please indicate name and date for any changes in this document.

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Title: A Pragmatic Effectiveness Trial: Safer Use of Antipsychotics in Youth (SUAY)

General Scientific Aim

The SUAY trial aims to minimize use of antipsychotics to treat non-psychotic behavioral disturbances in children in four real-world health care systems.

Specific Scientific Aim(s)

Our primary outcomes are percent of patients taking antipsychotic medication at 6 months post enrollment and total person-months of antipsychotic use by youth, based on medication order data. As a sensitivity analysis, we will also compare the percent of patients taking antipsychotic medication at 6 months post enrollment and total person-months of antipsychotic use by youth, based on prescription fill data.

Outcomes (dependent variable) of interest

Primary

i. % of patients taking antipsychotic medications (provider orders) at 6 months post enrollment
ii. Days of antipsychotic medication use (provider orders) during 6 months following enrollment

Secondary

i. Emergency department/urgent care visit frequency, both for psychiatric crises and for other reasons;
ii. Percentage of baseline and follow-up safety assessments (i.e., BMI measurement and laboratory orders);
iii. Percentage of clinicians with at least one change in AP treatment (AP discontinuation, treatment adjustment, and therapy referral);
iv. Modal stage at departure from algorithm (first line, second line, third line treatment prior to antipsychotic);
v. Last stage of patient treatment status
vi. Percent of patients that agree to behavioral health (BH) navigation;
vii. Percentage of patients attending two or more system-provided therapy sessions;
viii. Number of patients with any AP order

Predictor of interest: Treatment type (Intervention or Control)

We will compare the outcomes of patients initially prescribed an antipsychotic medication from intervention providers versus control providers. We plan to conduct an intent-to-treat analysis i.e. if a patient is enrolled when an intervention provider issues a qualifying prescription, the patient is enrolled in the intervention arm and, even if the patient sees a control provider at some point, the patient will remain in the intervention arm. Intervention arm is a binary treatment assignment that should be indicated for all enrolled patients in the analytic dataset.

Baseline Covariates

Baseline covariates for this study include: age, gender, race, ethnicity, site, type of insurance (Medicaid/Commercial/Other i.e. self-paid), any inpatient hospitalization in the prior year, provider type and new health plan enrollee (defined as person who does not have 2 or more encounters at least 60 days apart in the year prior to their prescription order date). This definition of new health plan enrollee will be compared to an alternate definition in the three sites with health plan enrollment data:< 105 days enrolled in the health care plan before randomization date). Note that gaps in enrollment less than 45 days count towards the total of 105. Gaps in enrollment >=45 days do not count towards the total of 105, nor does any enrollment prior to the gap >=45 days.
Any inpatient hospitalization in the prior year (-1 to -365 days from randomization date) will be adjusted for in primary analyses as it is prognostic of the outcome and will increase precision.

Health plan enrollment and follow-up time

Patient enrollment in the study occurs when a provider writes a qualifying antipsychotic prescription for an eligible adolescent patient or enters a patient reported medication (these two actions are indistinguishable in Epic). (Eligibility is confirmed by study staff following enrollment.) Follow-up time after enrollment extends for 6 months (181 days). Some patients will not remain enrolled in the health plan for a full six months, censoring follow-up, and the number of days covered in the health plan post-study enrollment should be recorded. If patients have a health care plan enrollment gap that is less than 45 days, they will be considered as having continuous enrollment in the study (i.e. not loss to follow up). For example, if a patient has a gap in their healthcare plan enrollment for less than 45 days during the study, this patient will be considered to have continuous enrollment. However, if there is an enrollment gap in their healthcare plan for at least 45 days, the patient will be disenrolled from the study at the healthcare plan disenrollment day. Note that, since patients do not have to be enrolled with a specific health care plan to be seen at NCH, we will assume a full follow up time of 6 months (181 days). Follow-up time should be indicated in the analytic dataset for all enrolled patients.

Analysis

Primary analysis I

Our primary analysis examines the percentage of patients taking antipsychotic medications (measured by provider medication orders) at 6 months post enrollment

Descriptive analysis will summarize **the percent of patients observed to be using AP at 6 months**, defined by presence of days' supply AP ≥ 181 days or medication in hand at 6 months. For example, if a patient has a 30-day supply order on or after 151 days post-enrollment, that patient has AP medication "in hand" at 6 months. Note: a patient does not have to have ≥ 181 days' total supply during the study to have medication in hand at 6 months. We will not adjust for loss to follow-up or disenrollment for this outcome definition. Patients who do not have prescription fill information up to 6 months post-baseline due to health plan disenrollment will have AP use observed at 6 months if they have AP orders after disenrollment that is >= 181 days. For example, if a patient disenrolls at day 160 and has a AP order (30 days' supply) after disenrollment, they have medication "in hand" at 6 months

Inferential analysis for this outcome will estimate **the odds ratio (OR) of AP use observed at 6 months** between intervention and control. For this analysis, we will use a logistic regression model where the outcome is a binary indicator of AP use observed at 6 months. Binary treatment arm assignment and any inpatient hospitalization in the prior year will be the only covariates

included in the regression model. The estimated coefficient associated with treatment is interpreted as the log-OR of observing AP use at six months for an intervention patient vs. a control patient. Patient is the unit of analysis, GEE will be used to account for correlation within provider, and robust standard errors (with working independence covariance matrix assumed) will be calculated to construct a 95% CI around the estimated OR. Our null hypothesis is that the OR is equal to 1, corresponding to no statistically significant difference between AP use observed at 6 months. We will reject the null hypothesis if the lower bound of the 95% CI is above 1 (increased use in treatment arm) or the upper bound is below 1 (decreased use in treatment arm).

Variables	Definition	Present/Absent
taking_at_6mon	Using AP at 6 months (No (0)/Yes(1))	present
groupn	Randomization Group – use for descriptive stats (Intervention (1)/Control(2))	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present

Sensitivity analysis will be conducted using similar approach as mentioned above, we will perform the following separate analyses related to our primary outcome by:

- % of patients taking antipsychotic medications (measured by orders) at 6 months post enrollment, using the minimum based on SIG reviews
- % of patients taking antipsychotic medications (measured by orders) at 6 months post enrollment, using the maximum based on SIG reviews
- % of patients taking antipsychotic medications (measured by prescription fills) at 6 months post enrollment. Note that this analysis may be performed using three healthcare systems (KPWA, KPCO, and KPNW) due to limitation in data availability

Variables	Definition	Present/Absent
taking_at_6mon_min	Using AP at 6 months – minimum (No (0)/Yes(1))	present
taking_at_6mon_max	Using AP at 6 months – maximum (No (0)/Yes(1))	present
taking_at_6mon_fills	Using AP (fills) at 6 months (No (0)/Yes(1))	present
groupn	Randomization Group – use for descriptive stats (Intervention (1)/Control(2))	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
site	Study site (KPCO (1)/KPWA (2)/KPNW(3)/NCH (4))	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present

- We will analyze outcome (orders) using adjusting for type of providers i.e. Mental Health (MH) providers in comparison to Non-Mental Health providers.

Variables	Definition	Present/Absent
taking_at_6mon	Using AP at 6 months (No (0)/Yes(1))	present

groupn	Randomization Group – use for descriptive stats (Intervention (1)/Control(2))	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present
provider_type	Provider type of the enrolling provider, based on specialty (Non-Mental Health (0)/Mental Health (1))	present

- We will adjust for some baseline covariates in the model – site only, site and age (since significantly different by intervention and controls), and site and baseline covariates.

Variables	Definition	Present/Absent
taking_at_6mon	Using AP at 6 months (No (0)/Yes(1))	present
group_cat	Randomization Group (Control (0)/Intervention (1))	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present
site	Study site (KPCO (1)/KPWA (2)/KPNW(3)/NCH (4))	present
provider_type	Provider type of the enrolling provider, based on specialty (Non-Mental Health (0)/Mental Health (1))	present
age_emanicip	Emancipated age according to state (No (0)/Yes(1))	present
gendern	Gender (Male (1)/Female (2))	present
race_AA	Either race variable is African American/Black (No (0)/Yes(1))	present
race_AllOth	All other racial/ethnic groups (does not include white, black or unknown) (No (0)/Yes(1))	present
Hispanic	Hispanic ethnicity (No (0)/ Yes (1))	Present
insuranceType	Type of insurance Commercial/Medicaid/Other	present
new_enrollee_1	new health enrollee (1st definition) Yes/No	present

Hypothesis-generating exploratory subgroup analysis will be the Heterogeneity of Treatment Effects (HTE), conducted using adjustment variables in the model. To perform HTE analyses, we will use the same analysis procedure for the primary outcome but now including adjustment variables indicated below separately, with an interaction term between the treatment and the covariate. HTE analyses are prespecified for: provider type (MH vs. non-MH), gender, age, race/ethnicity (composite variable), new health plan enrollee, insurance type (Medicaid vs. non-Medicaid) and whether participant had an exclusion diagnosis in year prior to baseline.

Variables	Definition	Present/Absent
taking_at_6mon	Using AP at 6 months (No (0)/Yes(1))	present
group	Randomization Group – use for restricted descriptive stats (Intervention/Control)	present
group_cat	Randomization Group	present

	(Control (0)/Intervention (1))	
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present
provider_type	Provider type of the enrolling provider, based on specialty (Non-Mental Health (0)/Mental Health (1))	present
age_emanicip	Emancipated age according to state (No (0)/Yes(1))	Present
gendern	Gender (Male (1)/Female (2))	Present
race_white_NH	Race - White non-Hispanic (only) (No (0)/Yes(1))	present
insuranceType	Type of insurance Commercial/Medicaid/Other	present
exclusion	Exclusion diagnosis in year prior to baseline	Needs to be created using baseline dx variables
new_enrollee_1	new health enrollee (1st definition) Yes/No	present
new_enrollee_2	new health enrollee (2nd definition) Yes/No	present

Primary analysis II

Our primary analysis examines antipsychotic medication (AP) use, as measured by days' supply ordered, in the 6 months following patient enrollment.

Descriptive analysis will summarize **the rate of AP use**, calculated as the days' supply (maximum of 181) ordered divided by follow-up time (time until end of enrollment or 181 days), Calculation of cumulative prescription fill ordered should be censored at 181 days. For example, if the only AP order for a patient is a 30 days' supply at, for e.g., 160 days post-enrollment, the total days' AP supply during follow-up should be recorded as 20 days (181 days -160 days) because we only want to capture AP use during the 6 months post-enrollment. In the case that total days' AP supply exceeds health plan enrollment that is, if a patient disenrolls from the health system with outstanding medication in hand, the total days' AP supply will include AP orders after disenrollment. For example, if a patient had an AP order after disenrollment on day 170 (a 30 days' supply), the total days' AP supply during follow-up should be recorded as sum of AP orders before day 170 and AP orders after day 170. Similarly, the offset should be increased to equal the last day with medication on hand (with a maximum for 181 for both).

Inferential analysis will estimate the **relative risk (RR) of AP use between intervention and control** during the 6 months post-enrollment. For this analysis, we will use Poisson regression where the outcome is the total days' AP supply (maximum of 181) for each enrolled patient and the offset is the number of days follow-up. For the primary analysis, treatment arm and inpatient hospitalization in the prior year will be the only covariates included in the regression model (additional covariate adjustment will be done as a sensitivity analysis), and the estimated coefficient for treatment arm is interpreted as the log-RR of AP use for an intervention patient vs. a control patient. Patient will be the unit of analysis for this regression model, and the regression model will be fit using generalized estimating equations (GEE) to account for correlation within provider. We will estimate standard errors using a robust (sandwich) covariance estimation (assuming a working independence covariance structure) and construct a 95% confidence interval (CI) around the estimated RR. Our null hypothesis is that the RR is equal to 1, corresponding to no statistically significant difference between AP order rates in

treatment and control patients. If the upper bound of the 95% CI is below 1, we will reject the null hypothesis and conclude that the RR of AP use is lower for intervention vs. control patients in the 6 months following enrollment (and vice-versa for a 95% CI above 1).

Variables	Definition	Present/Absent
person_days	Person-days on AP (orders) during 180 Day Follow-up Period (using orders)	present
group	Randomization Group – use for restricted descriptive stats (Intervention/Control)	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
p_offset	Number of days of follow-up for primary analysis (using orders)	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present

Sensitivity analysis will be conducted using similar approach as mentioned above, we will perform the following separate analyses related to our primary outcome by:

- Total person-months of antipsychotic medications (measured by orders) use by youth, based on minimum from SIGs review
- Total person-months of antipsychotic medications (measured by orders) use by youth, based on maximum from SIGs review
- Total person-months of antipsychotic medications (measured by prescription fills) use by youths. Note that this analysis may be performed using three healthcare systems (KPWA, KPCO, and KPNW) due to limitation in data availability

Variables	Definition	Present/Absent
person_days_min	Person-days on AP (orders) during 180 Day Follow-up Period (using orders) - minimum	present
person_days_max	Person-days on AP (orders) during 180 Day Follow-up Period (using orders) - maximum	present
person_days_fills	Person-days on AP (orders) during 180 Day Follow-up Period (using orders)	present
group	Randomization Group – use for restricted descriptive stats (Intervention/Control)	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
p_offset_min	Number of days of follow-up for primary analysis (using orders) - minimum	present
p_offset_max	Number of days of follow-up for primary analysis (using orders) - maximum	present
f_offset	Number of days of follow-up for primary analysis (using fills)	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present

- We will analyze outcome (orders) adjusting for type of providers i.e. Mental Health (MH) providers in comparison to Non-Mental Health providers

Variables	Definition	Present/Absent
person_days	Person-days on AP (orders) during 180 Day Follow-up Period (using orders)	present
group	Randomization Group – use for restricted descriptive stats (Intervention/Control)	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present

p_offset	Number of days of follow-up for primary analysis (using orders)	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present
provider_type	Provider type of the enrolling provider, based on specialty (Non-Mental Health (0)/Mental Health (1))	present

- We will adjust for some baseline covariates in the model – site only, site and age (since significantly different by intervention and controls), and site and baseline covariates.

Variables	Definition	Present/Absent
person_days	Person-days on AP (orders) during 180 Day Follow-up Period (using orders)	present
group_cat	Randomization Group Control (0)/Intervention (1)	present
p_offset	Number of days of follow-up for primary analysis (using orders)	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present
site	Study site (KPCO (1)/KPWA (2)/KPNW(3)/NCH (4))	present
provider_type	Provider type of the enrolling provider, based on specialty (Non-Mental Health (0)/Mental Health (1)	present
age_emanicip	Emancipated age according to state (No (0)/Yes(1))	present
gendern	Gender (Male (1)/Female (2))	present
race_AA	Either race variable is African American/Black (No (0)/Yes(1))	present
race_AllOth	All other racial/ethnic groups (does not include white, black or unknown) (No (0)/Yes(1))	present
Hispanic	Hispanic ethnicity (No (0)/ Yes (1))	Present
insuranceType	Type of insurance Commercial/Medicaid/Other	present
new_enrollee_1	new health enrollee (1st definition) Yes/No	present

- ~~Depending on the rate of cross-over, we will perform cross-over analysis that compares patients who switched from one provider in one arm to another provider in a different arm~~
- For the total number of days in the study, instead of using disenrollment date, we will use the date of the last encounter as the last day in study

Variables	Definition	Present/Absent
person_days	Person-days on AP (orders) during 180 Day Follow-up Period (using orders)	present
group_cat	Randomization Group (Control (0)/Intervention (1))	present
s_offset	Number of days of follow-up for sensitivity analysis (using last encounter date)	absent
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present

H*ypothesis-generating exploratory subgroup analysis* will be the Heterogeneity of Treatment Effects (HTE), conducted using adjustment variables in the model. To perform HTE analyses, we will use the same analysis procedure for the primary outcome but now including adjustment variables indicated below separately, with an interaction term between the treatment and the covariate. HTE analyses are prespecified for the same variables as below: provider type (MH vs. non-MH), gender, age, race/ethnicity (composite), new health plan enrollee status, insurance type (Medicaid vs. non-Medicaid) and whether participant had an exclusion diagnosis in year prior to baseline.

Variables	Definition	Present/Absent
person_days	Person-days on AP (orders) during 180 Day Follow-up Period (using orders)	present
group	Randomization Group – use for restricted descriptive stats (Intervention/Control)	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present
p_offset	Number of days of follow-up for primary analysis (using orders)	present
provider_type	Provider type of the enrolling provider, based on specialty (Non-Mental Health (0)/Mental Health (1)	present
age_emanicip	Emancipated age according to state (No (0)/Yes(1))	present
gendern	Gender (Male (1)/Female (2))	present
race_white_NH	Race - White non-Hispanic (only) (No (0)/Yes(1))	present
insuranceType	Type of insurance Commercial/Medicaid/Other	present
exclusion	Exclusion diagnosis in year prior to baseline	Needs to be created using baseline dx variables
new_enrollee_1	new health enrollee (1st definition) Yes/No	present
new_enrollee_2	new health enrollee (2nd defintion) Yes/No	present

Secondary analysis I

Emergency department visit/ Urgent care frequency, both for psychiatric crises and for other reasons

Definition: Number of emergency department visits and urgent care visits that occurred during the study, from the enrollment date to 6 months post-enrollment date

Inferential analysis: For these analyses, we have data that shows the frequency of emergency visits and frequency of urgent care separately, the outcomes. The main predictor is the treatment arm (intervention or control). We will have one record per patient, which shows the total number of ED or UC visits throughout the study (maximum of 6 months). We will perform Poisson regression analyses, where the outcome is the frequency of ED or UC visits for each enrolled patient and the offset is the number of days follow-up. The treatment arm and inpatient hospitalization in the prior year will be the only covariates included in the regression model, and the estimated coefficient for treatment arm is interpreted as the log-RR of visiting ED or UC more/less frequently, for an intervention patient vs. a control patient. Patient will be the unit of

analysis for this regression model, and the regression model will be fit using generalized estimating equations (GEE) to account for correlation within provider. We will estimate standard errors using a robust (sandwich) covariance estimation and construct a 95% confidence interval (CI) around the estimated RR. The estimated RR and two-sided confidence interval will be compared to the non-inferiority margin, M=1.5, and non-inferiority of the intervention will be concluded if the entire coverage of the 95% CI is less than 1.5.

Variables	Definition	Present/Absent
ed_uc	This is the number of days with emergency department and/or urgent care visits that occured during the study, from the enrollment date to 6 months post-enrollment	absent
group	Randomization Group – use for restricted descriptive stats (Intervention/Control)	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
e_offset	Number of days of follow-up for ED/UC analysis	absent
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present

Secondary analysis II

Percentage of youth with baseline and follow-up safety assessments (i.e., BMI measurement and laboratory measure/orders)
For these analyses, we will measure safety assessments of BMI and laboratory (Lipids, cholesterol, Hb1ac, prolactin, and any labs (at least 1)) measure/orders:

Definition I: BMI/laboratory measure/orders at baseline is defined as BMI/laboratory measure/orders observed in the 90 days before randomization and 7 days after randomization. BMI/laboratory during follow-up is defined as any BMI/laboratory measure/orders observed at least 30 days to +181 days following the randomization date. If no AP orders were made on the randomization date then these variables should be NA. The main predictor is the treatment arm (intervention or control). For these analyses, we will exclude those that did not have an AP order on randomization date.

We will perform 3 logistic regression analysis, where the outcome is a binary indicator of

i. BMI/Laboratory measure/orders entered at baseline (yes/no)
ii. BMI/Laboratory measure/orders entered at follow-up (yes/no)
iii. BMI/Laboratory measure/orders entered at baseline and follow-up (yes/no)

For these analyses, we will exclude those that did not have an AP order on randomization date.

Descriptive analysis will summarize **the percent of patients with observed BMI/Laboratory measure/orders at i, ii or iii**, defined above. For these analyses, we will exclude those that did not have an AP order on randomization date.

Inferential analysis: We will estimate the **odds ratio (OR) of BMI/Laboratory measure/orders observed at i or ii or iii,** between intervention and control. Binary treatment arm assignment will be the only covariate included in the regression model and the estimated coefficient is interpreted as the log-OR of observing BMI/Laboratory measure/orders at i or ii or iii, for an intervention patient vs. a control patient. Patient is the unit of analysis, GEE will be used to account for correlation within provider, and robust standard errors will be calculated to construct a 95% CI around the estimated OR. Our null hypothesis is that the OR is equal to 1, corresponding to no statistically significant difference between BMI/Laboratory measure/orders observed at i or ii or iii, for the treatment arms. We will reject the null hypothesis if the lower bound of the 95% CI is above 1 (increased BMI/Laboratory

measure/orders in treatment arm) or the upper bound is below 1 (decreased BMI/Laboratory measure/orders in treatment arm). For these analyses, we will exclude those that did not have an AP order on randomization date.

Variables	Definition	Present/Absent
groupn	Randomization Group – use for descriptive stats (Intervention (1)/Control(2))	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
bmi_baseline	0 = no, 1 = yes, 8 = NA	absent
bmi_fu	0 = no, 1 = yes, 8 = NA	absent
bmi_both	If bmi_baseline AND bmi_fu = 1, then 1 = yes, otherwise 0 = no; if no AP order on randomization date, then 8 = NA.	absent
lipids_baseline	0 = no, 1 = yes, 8 = NA	absent
lipids_fu	0 = no, 1 = yes, 8 = NA	absent
lipids_both	If lipids_baseline AND lipids_fu = 1, then 1 = yes, otherwise 0 = no; if no AP order on randomization date, then 8 = NA.	absent
chl_baseline	0 = no, 1 = yes, 8 = NA	absent
chl_fu	0 = no, 1 = yes, 8 = NA	absent
chl_both	If chl_baseline AND chl_fu = 1, then 1 = yes, otherwise 0 = no; if no AP order on randomization date, then 8 = NA.	absent
hb1ac_baseline	0 = no, 1 = yes, 8 = NA	absent
hb1ac_fu	0 = no, 1 = yes, 8 = NA	absent
hb1ac_both	If hb1ac_baseline AND hb1ac_fu = 1, then 1 = yes, otherwise 0 = no; if no AP order on randomization date, then 8 = NA.	absent
prolactin_baseline	0 = no, 1 = yes, 8 = NA	absent
prolactin_fu	0 = no, 1 = yes, 8 = NA	absent
prolactin_both	If prolactin_baseline AND prolactin_fu = 1, then 1 = yes, otherwise 0 = no; if no AP order on randomization date, then 8=NA.	absent
any_lab_baseline	0 = no, 1 = yes, 8 = NA	absent
any_lab_fu	0 = no, 1 = yes, 8 = NA	absent
any_lab_both	If any_lab_baseline AND any_lab_fu = 1, then 1 = yes, otherwise 0 = no; if no AP order on randomization date, then 8=NA.	absent

Secondary analysis III

Percentage of clinicians with at least one change in AP treatment (defined as AP discontinuation, treatment adjustment (change in other psychotropic medication), and therapy referral);

Definition: At least one of the following must occur to be flagged as 'Yes' or assigned the number 1

- AP discontinuation: no refills
- Medication adjustment i.e. non-AP mental health adjustment (either of the two below or both) by provider within 60 days of patient enrollment in study:
  - adding new psychotropic medication (including switching medications)
- Therapy referral by provider within 60 days of patient enrollment in study.
  - any new psychotherapy i.e. referral
- New mental health diagnosis (issued by the same provider) within 60 days of patient enrollment in study.

- At least one AP treatment change

Descriptive analysis will summarize **the percent of** clinicians with each type of change and at least one change in AP treatment (AP discontinuation, treatment adjustment, therapy referral, and new diagnosis), defined above.
Inferential analysis: We will estimate the **odds ratio (OR) of at least one change in AP treatment,** between intervention and control. Binary treatment arm assignment and prior hospitalization will be the only covariate included in the regression model and the estimated coefficient is interpreted as the log-OR of observing at least one change in AP treatment, for an intervention patient vs. a control patient. Patient is the unit of analysis, GEE will be used to account for correlation within provider, and robust standard errors will be calculated to construct a 95% CI around the estimated OR. Our null hypothesis is that the OR is equal to 1, corresponding to no statistically significant difference between the AP treatment, for the treatment arms. We will reject the null hypothesis if the lower bound of the 95% CI is above 1 (increased change in AP treatment in treatment arm) or the upper bound is below 1 (decreased change in AP treatment in treatment arm).

Variables	Definition	Present/Absent
groupn	Randomization Group – use for descriptive stats (Intervention (1)/Control(2))	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present
no_refill	if there exists a randate < rxdate for AP <= enddate or disenrollmentdate, then 0 = no, otherwise 1=yes	absent
new_med	0 = no new medication within [randate, randdate + 60 days], 1 = at least one new medication within [randate, randdate + 60 days]	absent
th_referral	0 = no new psychotherapy visit observed within [randate, randdate + 60 days], Otherwise, 1 = at least one new psychotherapy visit	absent
new_mh_dx	0 = no new mental health diagnosis, 1 = at least one new mental health diagnosis	absent
trt_change	If no_refills, new_med, th_referral, and new_mh_dx = 0, 0 = no AP treatment change, Otherwise 1 = at least one AP treatment change	absent

Secondary analysis IV

Modal stage at departure from algorithm (first line, second line, third line treatment prior to antipsychotic);

Definition: To assess this outcome, we will take account of the treatment(s) patients had before the BPA fired i.e. before the randomization date. These treatments have already been categorized into first line, second line and third line in the consensus panel document endorsed by the study psychiatrists and used to make suggestions regarding treatment changes.

Descriptive analysis will summarize **the percent of patients with first line, second line or third line** treatment algorithm departure.

No Inferential analysis will be done for this outcome.

Variables	Definition	Present/Absent
groupn	Randomization Group – use for descriptive stats (Intervention (1)/Control(2))	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
trt_line	0 = no treatment, 1 = first line, 2 = second line, 3 = third line	absent

Secondary analysis V (Intervention group only)

Last stage of patient treatment status

Definition: The last stage of patient treatment status takes accounts for patients when they stop at either the BPA firing, provider completed CAP consultation, navigation stage (consent status and number of calls), or tele-mental health (consent status and number of sessions)
Descriptive statistics will show the frequencies (sample size, percentages) of the last stage of patient treatment status at patient's study completion, as well as the mean and standard deviation of calls and TMH sessions for participants with any navigation calls or TMH sessions, respectively.

No inferential analysis will be performed for this outcome.

Variables	Definition	Present/Absent
trt_stage	If CAP_completed = pending, 1 = BPA If CAP_completed = completed, 2 = CAP If nav_status = agreed, 3 = NAV_C If max(n_nav_calls_delivered) > 0, then 4 = NAV_D If TMH_status = agreed, 5 = TMH_C If max(n_TMH_delivered) > 0, then 6 = TMH_D	present
trt_stage_n_nav_calls_delivered	Number of navigation calls delivered	Present
trt_stage_n_tmh_delivered	Number of telemental health delivered	Present

Secondary analysis VI (Intervention Group Only)

Percent of patients that agree to behavioral health (BH) navigation

Descriptive analysis will summarize **the percent of patients that agree to behavioral health (BH) navigation**

No inferential analysis will be performed for this outcome.

Variables	Definition	Present/Absent
accepts_nav	If nav_status= agreed	present

Secondary analysis VII

Percentage of patients attending two or more system-provided therapy sessions

Descriptive analysis will summarize **the percent of patients attending two or more system-provided therapy sessions**

Inferential analysis: We will estimate the **odds ratio (OR) of attendance to two or more system-provided therapy sessions between intervention and control.** The outcome will be

binary: two or more sessions (outcome=1) vs. fewer than two sessions (outcome=0). Binary treatment arm assignment and prior hospitalizations will be the only covariate included in the regression model and the estimated coefficient is interpreted as the log-OR of attending two or more system-provided therapy sessions, for an intervention patient vs. a control patient. Patient is the unit of analysis, GEE will be used to account for correlation within provider, and robust standard errors will be calculated to construct a 95% CI around the estimated OR. Our null hypothesis is that the OR is equal to 1, corresponding to no statistically significant difference between attending system-provided sessions, for the treatment arms. We will reject the null hypothesis if the lower bound of the 95% CI is above 1 (increased attendance to two or more system-provided therapy sessions in treatment arm) or the upper bound is below 1 (decreased attendance to two or more system-provided therapy sessions, in treatment arm).

Variables	Definition	Present/Absent
groupn	Randomization Group – use for descriptive stats (Intervention (1)/Control(2))	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
prior_hosp	Prior Hospitalization (No (0)/Yes(1))	present
th_sessions	defined as patients attending at least 2 system-provided therapy sessions (visits) throughout the study period	present

Secondary analysis VIII

Note: Data harvesting was not completed and this analysis was not conducted due to time constraints.

(i) Behavioral Change Analysis: Proportion of providers' patients with any AP order after BPA exposure during the study

(ii) Sustainment Analysis: Proportion of providers' patients with any AP order, both during and after the study

Note that: Intervention BPA gets turns off and Control Arm BPA turns on for both groups (July 1, 2020)

Behavioral Change Analysis:

Descriptive analysis will summarize the outcome distribution across providers. Within a provider, the outcome is **the percent of eligible patients with any AP order after the provider's first exposure to study** i.e., the first time the BPA fired. The first patient for whom the BPA fired (and enrolled in the study, if eligible) will not be counted in this analysis. After the first BPA firing, AP order will be recorded starting from the next "at risk" patient seen by the providers up until the end of the study enrollment. Note that most patients in the denominator for this outcome (at-risk patients) will not have an AP order and, thus, will not be enrolled in the study. "At risk" patients are defined as patients who meet eligibility criteria for the study i.e. patients who have the 13 diagnoses used for eligibility or the study, and do not have exclusion diagnoses (psychosis, mania, autism, developmental disability) or recent AP exposure used for ineligibility. The numerator and denominator for this outcome are patient counts: number of at-risk patients with any AP order / number of at-risk patients. Some at-risk patients may be seen multiple times by the provider, but they only contribute once to the numerator (any AP order, 0 or 1), and they only contribute one at-risk patient to the denominator. The numerator for each provider will be equal to the number of patients enrolled by that provider in the study.

Inferential analysis will estimate the **relative risk (RR) of prescribing an AP to an at-risk patient by intervention providers versus control providers after first exposure to study.**

For these analyses, we will use Poisson regression where the outcome is the number of patients with any AP order. The offset is the number of patients at risk. For this secondary analysis, treatment arm will be the only covariate included in the regression model, and the estimated coefficient is interpreted as the log-RR of number of patients with AP order from an intervention provider vs. a control provider. Provider will be the unit of analysis for this regression model, and the regression model will be fit using generalized linear model (GLM). We will construct a 95% confidence interval (CI) around the estimated RR. Our null hypothesis is that the RR is equal to 1, corresponding to no statistically significant difference between the number of patients with AP orders from treatment and control providers. If the upper bound of the 95% CI is below 1, we will reject the null hypothesis and conclude that the RR of prescribing AP to an "at risk" patient, is lower from the intervention vs. control providers, with a starting point after exposure to the BPA, until the end of the study enrollment (and vice-versa for a 95% CI above 1).

Sustainment Analysis:
Descriptive analysis will summarize the outcome distribution across providers. Within a provider, the outcome is **the percent of eligible patients with any AP order after July 1st 2020, with an ending time on December 31st 2020** i.e., the first time the Control BPA is fired for both the Intervention and Control arms. (Note that July 1st, 2020 – December 31st, 2020 is defined as the post period, while time on study i.e. before July 1st 2020, is defined as the pre period). After the first BPA firing, AP order will be recorded starting from the "at risk" patient seen by the providers up until December 31st, 2020. Note that most patients in the denominator for this outcome (at-risk patients) will not have an AP order and, thus, will not be enrolled in the study. "At risk" patients are defined as patients who meet eligibility criteria for the study i.e. patients who have the 13 diagnoses used for eligibility or the study, and do not have exclusion diagnoses (psychosis, mania, autism, developmental disability) or recent AP exposure used for ineligibility. The numerator and denominator for this outcome are patient counts: number of at-risk patients with any AP order/ number of at-risk patients, stratified by pre and post periods. Some at-risk patients may be seen multiple times by the provider, but they only contribute once to the numerator (any AP order, 0 or 1), and they only contribute one at-risk patient to the denominator. The numerator for each provider will be equal to the number of patients enrolled by that provider in the study.
Inferential analysis will estimate the **relative risk (RR) of prescribing an AP to an at-risk patient by intervention providers versus control providers after first exposure to study.** For this analysis, we will use Poisson regression where the outcome is is the number of patients with any AP order after July 1st, 2020. For this secondary analysis, treatment arm will be the only covariate included in the regression model, and the estimated coefficient is interpreted as the log-RR of number of patients with AP order from an intervention provider vs. a control provider. Provider will be the unit of analysis for this regression model and the regression model will be fit using generalized estimating equations (GEE) to account for correlation within provider. We will estimate standard errors using a robust (sandwich) covariance estimation (assuming a working independence covariance structure) and construct a 95% confidence interval (CI) around the estimated RR. An interaction term between treatment and the time period (pre versus post) will give us the estimates. Our null hypothesis is that the RR is equal to 1, corresponding to no statistically significant difference between AP order rates in treatment vs. control patients in the post period. If the upper bound of the 95% CI is below 1, we will reject the null hypothesis and

conclude that the RR of AP use is lower for intervention vs. control patients in the post period (and vice-versa for a 95% CI above 1).

Variables	Definition	Present/Absent
pid	provider type based on specialty	present
groupn	Randomization Group – use for descriptive stats (Intervention (1)/Control(2))	present
group_cat	Randomization Group – use in models (Control (0)/Intervention (1))	present
provider_type	This is the total number of eligible patients with at least one AP order, seen by each provider, starting from July 1st 2020 to December 31st 2020	present
n_pt_pre	The total number of "at-risk" patients that would have been enrolled in the study if the provider would have prescribed AP, before July 1st 2020	variable absent, value absent
n_pt_post	The total number of "at-risk" patients that would have been enrolled in the study if the provider would have prescribed AP, starting from July 1st 2020 to December 31st 2020	variable absent, value absent
pre_offset	The total number of "at-risk" patients that would have been enrolled in the study if the provider would have prescribed AP, before July 1st 2020	variable absent, value absent
post_offset	This is the total number of eligible patients with at least one AP order, seen by each provider, before July 1st 2020	variable absent, value absent