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Comparison of antipsychotic prescribing practices following failure of antipsychotic monotherapy in the acute care setting

Kaitlyn Morgan, PharmD, BCPP[1]
Leah Rickert, PharmD, BCPP[2]

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Abstract

Introduction: Numerous strategies exist following antipsychotic monotherapy failure including transition to another antipsychotic, dosing above FDA recommendations, or dual antipsychotic therapy. This study described antipsychotic prescribing practices on an acute psychiatry unit following antipsychotic monotherapy failure and compared outcomes to determine if any strategy resulted in superior short-term outcomes.

Methods: This retrospective chart review assessed postintervention time to discharge for patients with schizophrenia or schizoaffective disorder requiring therapy change following treatment failure. Secondary outcomes included 30-day readmission rate, length of stay, and discharge chlorpromazine equivalents.

Results: There were no differences in number of past antipsychotic trials between groups (4.8 vs 4.5; $P = .73$). Of all the patients, 73% (n = 30) discharged on alternative antipsychotic monotherapy while 27% (n = 11) discharged on dual antipsychotic therapy. No patients had doses increased above FDA recommendations. The alternative antipsychotic group had shorter mean postintervention time to discharge (8.8 vs 20.6 days; $P = .003$) and shorter mean length of stay (16.7 vs 32.1 days; $P = .03$). Median time to discharge was not statistically significant (6.4 vs 14.0 days; $P = .17$). The dual antipsychotic group had higher mean chlorpromazine equivalents (723 mg vs 356 mg; $P = .002$). There was no difference in 30-day readmission rates (16.7% vs 27.3%; $\chi^2 = 0.5765$; $P = .45$).

Discussion: This study found that following failure of antipsychotic monotherapy, transition to an alternative antipsychotic was associated with decreased mean time to discharge as compared to dual antipsychotic therapy. Further studies are needed to assess long-term clinical implications of these findings.

Keywords: antipsychotics, schizophrenia, acute care, dual antipsychotics

[1] (Corresponding author) Clinical Pharmacy Practitioner in Behavioral Health, Doris Miller Department of Veterans Affairs Medical Center, Waco, Texas, kaitlyn.morgan@va.gov, ORCID: https://orcid.org/0000-0003-3888-9637; [2] Psychiatric Clinical Pharmacy Specialist, Doris Miller Department of Veterans Affairs Medical Center, Waco, Texas, ORCID: https://orcid.org/0000-0002-9157-8646

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Introduction

Antipsychotic monotherapy is recommended for treatment of acute phase schizophrenia.[1-4] Unfortunately, many patients in acute care settings experiencing their first episode of schizophrenia will not respond well to initial antipsychotic therapy. Of these patients, 81% will achieve a 20% or greater reduction in schizophrenia symptoms. However, only about half of patients will achieve at least a 50% reduction in symptoms.[5] Rates of response to antipsychotic therapy during acute phase schizophrenia decrease even further in patients with chronic schizophre-

nia, with about half of patients achieving a 20% or greater reduction in symptoms and 23% achieving at least a 50% reduction.[6] Poor response to an antipsychotic and exacerbation of symptoms leading to hospitalization typically necessitates an adjustment to current therapy. Multiple strategies are used in practice following failure of antipsychotic monotherapy, including transition to another single antipsychotic, use of doses higher than FDA recommendations, or use of dual antipsychotic therapy.[1-4] Available data[5-7] shows a lack of high-quality, randomized controlled studies to support the practice of polypharmacy with dual antipsychotics. Guidelines[1-4] recommend use of doses higher than FDA recommendations or dual antipsychotic therapy for only short-term treatment of acute phase schizophrenia. Antipsychotic monotherapy is preferred because of concerns for drug-drug interactions, poor adherence, higher costs, and increased risk of adverse events with dual antipsychotic therapy.

Previous retrospective studies[8-10] have evaluated patterns of antipsychotic prescribing in the Veterans Affairs' system. While providing information on real-world practices and identifying populations most likely to receive these interventions, these studies have not examined the practices in relation to clinical outcomes. The current study aims to (1) describe local antipsychotic prescribing practices on the acute psychiatry unit following failure of antipsychotic monotherapy, and (2) compare treatment outcomes between practice strategies using time to discharge following intervention as a proxy for time to clinical stabilization.

Methods

This medication use evaluation used a retrospective chart review study design and was categorized as a quality improvement project and thus was exempt from IRB approval. Patients included in this review were at least 18 years old and admitted to an acute psychiatry unit of a Veterans Affairs' hospital between January 1, 2018 and December 31, 2019, with a principal diagnosis of schizophrenia or schizoaffective disorder per *ICD-10* diagnostic codes. The initial patient list was identified using logic from tables found in the Veterans Affairs Corporate Data Warehouse. Query logic was based on 2 cohorts: patients discharged from acute psychiatry units between January 1, 2018 and December 31, 2019, and outpatient prescriptions released between December 27, 2017 and January 2, 2020, limited by medications designated in the Veterans Affairs Class for antipsychotics.

Patients eligible for inclusion had one of the following changes to antipsychotic therapy made during hospitalization: change to different antipsychotic agent as monotherapy, augmentation with a second antipsychotic agent, or increase in antipsychotic dose to exceed FDA recommendations.

Patients were excluded from analysis if they had antipsychotic therapy changed due to a reason other than treatment failure or partial response. Reason for admission antipsychotic discontinuation was determined based on the indication for discontinuation selected in the electronic health record by the provider at the time of discontinuation. Failure of antipsychotic medications was declared if (1) the provider selected an option other than *adverse drug reaction to therapy*, *duplicate order*, *entered in error*, *nonadherence to follow-up/monitoring*, or *patient refuses*, (2) provider selected the option *failure to respond*, or (3) provider selected the option of *no longer indicated or obsolete order* if another antipsychotic agent was ordered without documentation of an adverse drug reaction or nonadherence in the corresponding progress note. Reason for therapy change was confirmed through chart review. Patients with mention of medication nonadherence prior to admission were excluded from analysis, as were patients who requested to change antipsychotic therapy for any reason aside from treatment failure or for whom therapy was changed due to reported adverse drug reactions. Patients were also excluded if they did not have antipsychotic medication changes during their inpatient admission, were not on an antipsychotic prior to admission to the inpatient unit, or were already on multiple antipsychotics at the time of admission. Patients who discharged against medical advice or to the inpatient medical unit were also excluded.

Patients were assigned to 1 of 3 treatment groups based on the type of change to antipsychotic therapy made during hospitalization, as defined above. Patients who were discharged prior to completion of documented cross-titration from one antipsychotic to another were included in the alternative monotherapy group given that this was the providers intent. The primary outcome of this study was time to discharge after medication intervention as an indicator of time to stabilization. Secondary outcomes include 30-day readmission rate, total length of stay, and total antipsychotic burden reported as chlorpromazine (CPZ) equivalents at discharge. CPZ equivalents were calculated using the Psychopharmacopeia Antipsychotic Dose Conversion Calculator.[11]

Continuous data was analyzed using independent *t* tests, and categorical data was analyzed using χ^2. Given wide ranges observed with the continuous data collected in this study, statistics for primary and secondary outcomes were also completed using Mann-Whitney *U* test to account for non-normal distribution of data. Significance level of 0.05 was used for all χ^2 and Mann-Whitney *U* test calculations.

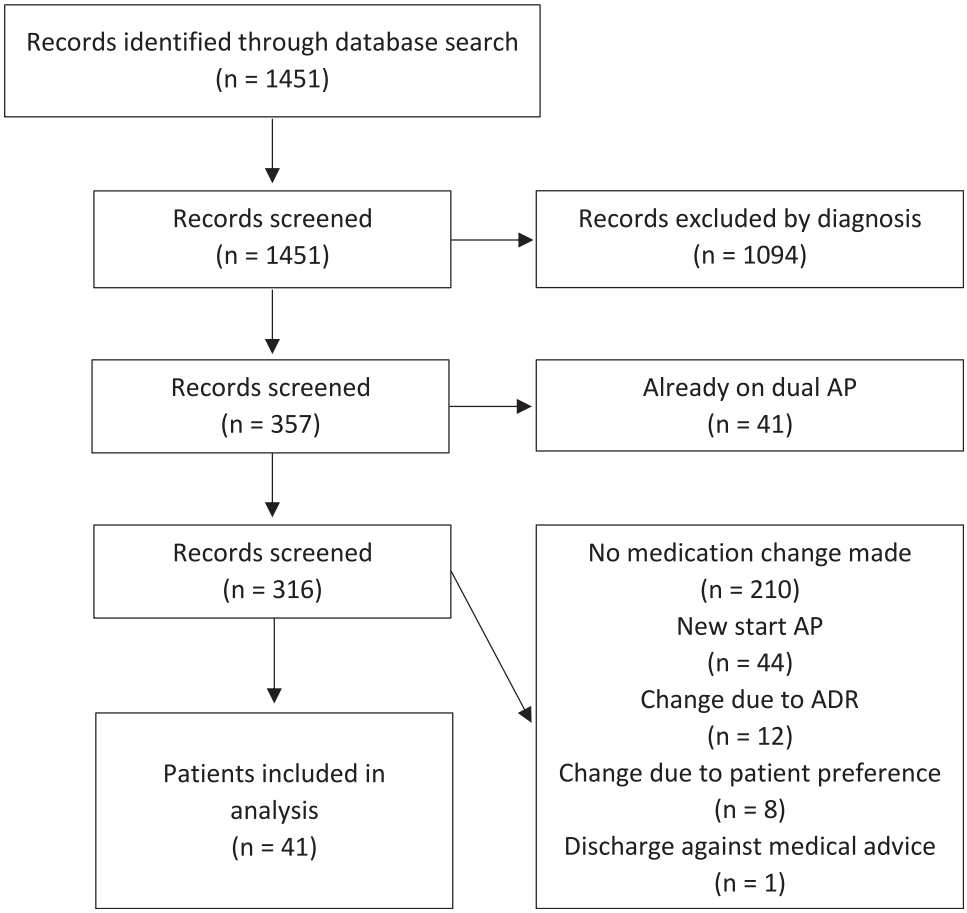

FIGURE: Inclusion and exclusion flow diagram (ADR = adverse drug reaction; AP = antipsychotic)

Results

From the initial data pull 1451 patients were identified with only 350 patients screened for inclusion based on a principal diagnosis of schizophrenia or schizoaffective disorder. Of those, 41 patients met criteria for inclusion and were reviewed (Figure). Baseline demographic characteristics for each intervention group are reported in Table 1. The majority of patients included were white (56%), male (88%), and had a principal diagnosis of schizoaffective disorder (66%). There were no significant differences between study groups for average number of previous antipsychotic trials (4.8 vs 4.5; $P = .73$) or mean time to intervention (7.8 days vs 11.7 days; $P = .40$).

Following failure of antipsychotic monotherapy, 30 patients (73.2%) were transitioned to an alternative antipsychotic as monotherapy, 11 patients (26.8%) were augmented with an additional antipsychotic medication, and no patients had doses increased to greater than FDA recommendations. The alternative antipsychotic group had a mean time to discharge following medication adjustment of 8.8 days compared to 20.6 days in the dual antipsychotic group ($P = .003$; 95% CI = −18.9, −4.7). Median time to discharge following medication adjustment was 6.4 days for the alternative antipsychotic group vs 14.0 days in the dual antipsychotic group ($P = .17$; $z = -1.37$). The alternative antipsychotic group also had a significantly shorter mean length of stay (16.7 days) than the dual antipsychotic group (32.1 days; $P = .03$; 95% CI = −28.4, −2.4). Length of stay remained significantly shorter in the alternative antipsychotic group (9.5 days) vs the dual antipsychotic group (40.0 days) when median length of stay was assessed ($P = .02$; $z = -2.43$). The occurrence rate of 30-day readmission was not statistically significant between the 2 groups (16.7% vs 27.3%; $\chi^2 = 0.5765$; $P = .45$). Antipsychotic burden per mean CPZ equivalents was significantly lower in the alternative antipsychotic group (356 mg) vs the dual antipsychotic group (723 mg; $P = .001$; 95% CI = −586.8, −144.8). Median antipsychotic burden was not significantly different between the two groups (400 mg vs 500 mg; $P = .07$; $z = -1.81$). A full comparison of outcomes along with applicable statistical analysis are reported in Table 2.

Discussion

Following failure of antipsychotic monotherapy, a majority of patients (73%) in the study population were transitioned

TABLE 1: Baseline characteristics of the study[a]

	Alternative AP, n (%) N = 30	Dual AP, n (%) N = 11	Statistical Analysis
Mean age, y (range)	48 (29-70)	49 (30-71)	$P = .82$
Gender			
Male	25 (83.3)	11 (100)	$\chi^2 = 0.4861$; $P = .49$
Female	5 (16.7)	0 (0)	
Race			
Black	9 (30)	3 (27.3)	$\chi^2 = 1.9649$; $P = .37$
White	18 (60)	5 (45.5)	
Other/Unknown	3 (10)	3 (27.3)	
Diagnosis			
Schizophrenia	12 (40)	2 (18.2)	$\chi^2 = 1.7039$; $P = .19$
Schizoaffective disorder	18 (60)	9 (81.8)	
Mean previous AP trials, n (range)	4.8 (1-8)	4.5 (1-9)	$P = .73$
Mean time to intervention, d (range)	7.8 (0-50)	11.7 (2-32)	$P = .40$

AP = antipsychotic.

[a]Above FDA-recommended dose group was excluded from this table since n = 0.

to an alternative antipsychotic as monotherapy. This was in alignment with current guideline recommendations for the treatment of acute psychosis. The remaining 27% of patients were discharged on dual antipsychotic medications without documented plan for cross-titration. This rate is higher than that seen in a large-scale study done in 2016 looking at patients discharged from an inpatient psychiatric state hospital. Of the 58 611 patients in the study who were discharged on an antipsychotic, 18.4% were discharged on dual antipsychotics.[12] No patients included in this study had the antipsychotic they were on at the time of admission increased to a dose above FDA-recommended maximum doses. This was unexpected given that this is reported commonly enough in clinical practice to be included in guidelines as a potential short-term option. A 2002 United Kingdom study[13] of 3132 patients receiving antipsychotics found that 5.5% were taking a single antipsychotic at a dose above *British National Formulary* guidance.

Notably there was no significant difference between groups at baseline for mean number of previous antipsychotic trials. The scope of this study did not assess patients for treatment resistance, defined as 2 or more trials of antipsychotic medications at adequate dose and duration with documented adherence, since past medications trials were not evaluated in detail. However, 92.6% of the study population had been prescribed at least 2 different antipsychotics prior to study admission. Of the patients with 2 or more past

TABLE 2: Primary and secondary outcomes of the study

	Alternative AP N = 30	Dual AP N = 11	Statistical Analysis[a]
Primary Outcomes			
Mean time to discharge postintervention, d (range)	8.8 (1-37)	20.6 (1-43)	**$P = .003$; 95% CI = −18.9, −4.7**
Median time to discharge postintervention, d (range)	6.4 (1-37)	14.0 (1-43)	$P = .17$; z = −1.37
Secondary Outcomes			
Mean length of stay, d (range)	16.7 (3-85)	32.1 (6-59)	**$P = .03$; 95% CI = −28.4, −2.4**
Median length of stay, d (range)	9.5 (3-85)	40 (6-59)	**$P = .02$; z = −2.43**
Mean CPZ equivalent, at discharge, mg (range)	356 (100-800)	723 (75-1750)	**$P = .001$; 95% CI = −586.8, −144.8**
Median CPZ equivalent, at discharge, mg (range)	400 (100-800)	500 (75-1750)	$P = .07$; z = −1.81
30-d Readmission, n (%)			
Yes	5 (16.7)	3 (27.3)	$P = .45$; $\chi^2 = 0.5765$
No	25 (83.3)	8 (72.7)	

AP = antipsychotic; CPZ = chlorpromazine.

[a]Boldface type indicates statistically significant difference between groups ($P < .05$).

antipsychotic trials, 4 (10.5%) were transitioned to clozapine during admission and discharged on clozapine with or without an augmenting agent. One patient was admitted on clozapine and transitioned to an alternative agent during their admission. Additional information on admission and discharge medications can be found in Table 3.

No advantage for dual antipsychotic therapy over switching to alternative antipsychotic as monotherapy was seen in this study. Switching to an alternative antipsychotic agent was associated with a shorter mean time to discharge following intervention and shorter mean total length of stay compared to dual antipsychotic therapy. Statistical analysis was also completed using median values to account for the high intergroup variability in time to discharge following intervention and length of stay. Median value statistics did not show a statistically significant difference in time to discharge postintervention between the 2 groups (6.4 vs 14.0; $P = .17$). The dual antipsychotic group did have a longer median time to discharge postintervention of over 7 days which, while not statistically significant, is a clinically relevant increase. Median length of stay remained significantly higher in the dual antipsychotic group (40.0 days vs. 9.5 days; $P = .02$; $z = -2.43$). The longer median length of stay seen in the dual antipsychotic group may suggest a higher acuity of illness which may have impacted provider decision to add an additional antipsychotic to treatment regimen as opposed to transitioning to an alternative antipsychotic as monotherapy. No difference in 30-day readmission rates were found between groups.

CPZ equivalents of greater than 1000 mg is traditionally considered high or excessive dosing, which may put the patient at increased risk of adverse drug reactions or toxicity.[14] The dual antipsychotic group had a higher mean antipsychotic burden based on CPZ equivalents at time of discharge. However, median antipsychotic burden was not significantly different between the 2 groups. Neither mean nor median CPZ equivalents fell above the excessive dosing range. This finding suggests that when abnormal distribution of data is taken into account, the dual antipsychotic group did not have statistically significant higher antipsychotic burden.

Because of the nature of the retrospective chart review design, it was unclear why providers chose one strategy over another. One potential reason for choosing augmentation with a second antipsychotic over switch to an alternative agent may be severity of acute illness at time of presentation. The finding that median total length of stay remained significantly higher in the dual antipsychotic group when accounting for non-normal distribution supports this possibility. This study did not assess baseline disease or symptom severity, which is a limitation of study design and may be a source for confounding. Another limitation of this study as a result of its retrospective design is risk of inconsistent or incomplete documentation in the electronic health record which could potentially affect the validity of patients selected for inclusion into the study and assignment of patients to treatment groups. To account for the effects of incomplete or inconsistent documentation of reason for discontinuation of medication in the providers progress note, reason for discontinuation of initial antipsychotic therapy was determined using the option selected by the provider at the time the medication order was discontinued.

This study was limited by its specific patient population within a Veterans Affairs' hospital as well as the small sample size. Given that this study was conducted within the Veterans Affairs, generalizability to other clinical settings may be limited. Hospitalizations for patients discharged with a principal diagnosis of schizophrenia or schizoaffective disorders accounted for only 24% ($n = 357$) of admissions resulting in discharge on an antipsychotic during the study period. Of those, only 19% ($n = 61$) required a change in antipsychotic medications, of which not all were because of antipsychotic failure. Inability to assume medication adherence prior to admission is an additional limitation of this study. The majority of patients were continued or restarted on previous antipsychotic medications or had doses titrated within FDA-recommended doses. Continuation of previous antipsychotic during an acute exacerbation of schizophrenia symptoms could indicate a lack of medication adherence in the outpatient setting contributing to a large number of the admissions in this study population. This is consistent with existing literature, which shows that up to 56% of patients with schizophrenia become nonadherent to their psychotropic medications.[10]

There is pressure to discharge a patient from acute care as soon as criteria for admission are no longer met in order to ensure appropriate use of resources and to ensure care is being delivered in the appropriate environment. Occasionally, patients are discharged once they no longer meet criteria of admission even if new medications have not been fully titrated or cross-tapered with the expectation that the titration or cross-taper will be continued by the outpatient provider. For the purposes of this study, patients who were discharged prior to completion of cross-tapering from one antipsychotic to another were included in the alternative antipsychotic group if there was clear documentation in the providers discharge summary that the cross-taper was intended to be continued in the outpatient setting. However, there is a possibility that patients intended to be cross-tapered but did not have appropriate documentation were included in the dual antipsychotic group inappropriately. This would have falsely increased the number of patients reported in the dual antipsychotic group.

TABLE 3: Select patient characteristics

ID	Sex	Age (yrs)	Race	Dx	Admit AP	Previous AP trials	Discharge AP	CPZ Equivalent, mg	Time to Intervention, d	LOS, d
1	F	46	Black	SZA, unspecified	RIS	2	OLZ	500	2.61	10
2	M	38	White	SZA, bipolar type	HAL	6	RIS	400	0.34	6
3	M	66	White	SZA, bipolar type	RIS	8	RIS + PAL[a]	418	16.94	22
4	M	30	White	Schizophrenia, unspecified	OLZ	3	QUET	675	4.08	12
5	M	39	Unknown	Paranoid schizophrenia	RIS	1	LOX	200	0.61	7
6	M	66	White	Paranoid schizophrenia	QUET	2	ARI	125	1.56	8
7	M	58	White	SZA, bipolar type	QUET	5	LUR	100	1.40	3
8	M	35	Unknown	SZA, bipolar type	RIS	5	HAL + RIS	500	2.70	10
9	M	35	Unknown	SZA, bipolar type	OLZ	5	RIS + OLZ	400	2.00	6
10	M	47	Black	SZA, bipolar type	QUET	5	HAL + QUET	500	32.26	40
11	M	71	White	Paranoid schizophrenia	OLZ	1	OLZ + FLU	1500	8.73	46
12	M	29	White	SZA, bipolar type	ZIP	3	RIS + PAL[a]	208	3.83	13
13	M	62	Black	Schizophrenia, unspecified	RIS	5	QUET	275	0.08	6
14	M	40	White	Paranoid schizophrenia	QUET	3	OLZ	500	5.76	21
15	M	56	Unknown	SZA, bipolar type	OLZ	2	RIS	400	1.23	5
16	M	34	Asian	Paranoid schizophrenia	ARI	1	ARI + OLZ	200	18.00	19
17	M	71	Black	SZA, bipolar type	OLZ	8	LUR + RIS	1750	7.78	41
18	M	70	White	SZA, bipolar type	PAL	8	OLZ	500	0.64	17
19	M	42	White	SZA, depressive type	RIS	2	OLZ	100	1.68	6
20	M	30	Black	Paranoid schizophrenia	PAL	2	RIS + PAL[a]	400	0.56	6
21	M	57	Black	Schizophrenia, unspecified	RIS	7	OLZ	400	0.21	7
22	M	59	Black	Disorganized schizophrenia	PER	7	RIS + PAL[a]	418	1.69	21
23	M	63	White	SZA, depressive type	RIS	5	CLZ + HAL	1250	15.29	59
24	M	48	Black	SZA, bipolar type	PAL	4	OLZ	600	0.16	15
25	M	60	White	SZA, bipolar type	QUET	9	CLZ + OLZ	900	7.08	47
26	M	58	Black	SZA, bipolar type	ZIP	8	HAL	179	1.98	8
27	M	66	White	SZA,ipolar type	OLZ	4	ARI	200	50.38	61
28	M	60	White	SZA, bipolar type	QUET	6	HAL + QUET	500	5.83	20
29	M	42	White	SZA, bipolar type	QUET	7	RIS	400	0.85	10
30	F	36	Black	SZA, bipolar type	ZIP	3	LOX + ZIP[a]	500	39.55	44
31	M	66	White	Schizophrenia, unspecified	QUET	4	RIS	100	1.00	6
32	M	32	White	Schizophrenia, unspecified	QUET	3	OLZ	200	0.09	6
33	M	70	White	Paranoid schizophrenia	CLZ	8	HAL	500	10.75	17
34	M	70	White	SZA, bipolar type	OLZ	8	CLZ	800	28.10	42
35	M	35	Unknown	SZA, bipolar type	ZIP	5	OLZ	100	0.76	4
36	M	36	White	SZA, bipolar type	OLZ	2	HAL + OLZ	375	21.62	55
37	M	30	Black	SZA, depressive type	PAL	3	QUET + PAL	75	7.76	10
38	F	29	White	SZA, unspecified	ZIP	7	LUR	400	1.66	9
39	F	29	White	SZA, bipolar type	LUR	7	ZIP	200	0.25	7
40	F	29	White	SZA, unspecified	QUET	6	ZIP	275	7.68	18
41	M	44	Black	Disorganized schizophrenia	LOX	5	CLZ	600	47.00	85

AP = antipsychotic; ARI = aripiprazole; CLZ = clozapine; CPZ = chlorpromazine; Dx = diagnosis; FLU = fluphenazine; HAL = haloperidol; LOS = length of stay; LOX = loxapine; LUR = lurasidone; OLZ = olanzapine; PAL = paliperidone; PER = perphenazine; QUET = quetiapine; RIS = risperidone; SZA = schizoaffective disorder; ZIP= ziprasidone.

[a]Documented plan for cross-taper between agents; included in alternative antipsychotic group.

Conclusion

This study found that local antipsychotic prescribing patterns are consistent with guideline recommendations for the treatment of acute phase schizophrenia and schizoaffective disorder. Rate of dual antipsychotic prescribing was higher in this study population than is seen in recent literature. No advantage to dual antipsychotic therapy was found. Based upon outcomes examined in this study, patients transitioned to an alternative antipsychotic had better short-term clinical outcomes evidenced by a shorter mean time to discharge following intervention and shorter mean and median overall length of stay. Median time to discharge was not statistically different between groups but was clinically relevant. Future studies evaluating long-term safety and efficacy outcomes in those using dual antipsychotic therapy are needed to assess the best treatment following antipsychotic monotherapy failure.

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