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Start low, go fast? Antipsychotic titration patterns at an inpatient psychiatric hospital

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Abstract

Introduction: Antipsychotics are commonly used to treat psychotic symptoms and severe mental illnesses. Treatment guidelines recommend antipsychotics be titrated quickly to therapeutic effect in the acute setting but acknowledge that determining the optimal dose is complicated by a delay between treatment initiation and therapeutic response. The purpose of this study was to evaluate antipsychotic titration patterns in an inpatient psychiatric hospital.

Methods: This study is a retrospective chart review of adult patients admitted to a teaching hospital and initiated on an antipsychotic for treatment of psychosis between January and December 2018. Patients were excluded if they had substance-induced psychosis, delirium, were prescribed >1 antipsychotic, or had no antipsychotic dose changes. The primary outcome was the average titration rate of the newly initiated antipsychotic. Secondary outcomes included differences in titration rate between involuntary and voluntary admissions and other antipsychotic characteristics.

Results: Of 149 patients included, the majority had a primary diagnosis of schizophrenia. Antipsychotics were titrated on average every 2 days regardless of admission type. Eighteen percent of patients were titrated to guideline-recommended maximum doses, and it took, on average, 3 days for patients to reach their final dose during hospitalization. Average length of stay was 9 days, and 43.6% of patients were readmitted within 1 year.

Discussion: Antipsychotics are titrated rapidly in the inpatient setting despite a lack of evidence regarding the impact of titration rate on clinical outcomes. Further studies comparing slow versus rapid titration strategies are needed to elucidate the impact of this on patient outcomes.

Keywords: antipsychotic, titration, inpatient, psychiatry, hospital

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Introduction

Antipsychotics are commonly used to treat psychotic symptoms and severe mental illnesses.[1-3] Antipsychotic selection and dosing is determined based on treatment indication, prior treatment response, side-effect profile, comorbid medical conditions, drug interactions, and cost.[3,4] Adverse effects, such as extra-pyramidal symptoms (EPS), are often dose-dependent.[5-8] Therefore, it's important to monitor closely for both tolerability and efficacy with each dose increase because issues with both can lead to medication nonadherence,[9] the most common cause of psychotic relapse.[10]

Unfortunately, medication nonadherence and episodic relapses are common in patients with serious mental illness.[11,12] Evidence shows that the longer patients experience untreated psychosis, the poorer their prognosis becomes.[13,14] Therefore, treatment guidelines recommend acute pharmacologic treatment be initiated promptly and the dose be titrated as quickly as tolerated to the target therapeutic dose.[2,3,15] However, determining the target therapeutic dose is complicated by the unpredictability in the time it takes individuals to achieve treatment response. For patients with severe mania or schizophrenia, it may take up to 2 weeks to show an improvement in symptoms[3,10] and even longer for patients with a history of more relapses. This would suggest that treatment could take at least a few weeks for patients admitted for acute decompensation. Although the goals of treatment during the acute phase are to prevent harm, reduce symptom severity, reestablish baseline functioning, and minimize the risk for relapse, they are also to stabilize individuals quickly to reduce length of stay and minimize health care costs.[2,3] This makes determining each patient's therapeutic dose difficult because treatment effects are generally delayed with each dose increase. Although treatment may need to be more aggressive during the acute treatment phase, it's also important to consider the potential for delayed adverse effects that may occur if dose increases occur sooner than necessary. This is also important to consider before administering long-acting injectable (LAI) antipsychotic formulations, which may be used in acute treatment settings to improve treatment adherence. Administering LAIs without allowing sufficient time to establish tolerability and efficacy with the oral formulation could also lead to delayed adverse effects or rehospitalization.

Although guidelines recommend titrating antipsychotics as quickly as tolerated to therapeutic doses, they also caution against premature dose escalations to allow sufficient time for monitoring treatment response.[2,3] There is no clear definition as to what constitutes a sufficient amount time for monitoring treatment response; however, most antipsychotics have an average half-life of 1 day or longer, meaning it can take up to 5 days or more for patients to reach steady-state concentrations once a target dose is reached. Given that dose titrations are based on clinical discretion, it is important to evaluate current antipsychotic titration patterns in the acute treatment setting. Because there are currently no studies available on this topic, the purpose of this study was to investigate antipsychotic titration patterns at a free-standing psychiatric facility.

Methods

This was a retrospective chart review conducted at the Behavioral Health Pavilion of Banner University Medical Center South (BUMCS), which is a 66-bed inpatient psychiatric facility in southern Arizona that accepts patients requiring involuntary admission due to being a danger to self/others (DTS/DTO) or persistently acutely disabled (PAD) secondary to a severe mental illness. Patients admitted between January 2018 and December 2018 with a documented primary discharge diagnosis of either a schizophrenia spectrum disorder, mood disorder with psychotic features, or unspecified psychosis that were initiated on an antipsychotic and received subsequent dose increases during the same hospital admission were included. Patients were excluded if they had substance-induced psychosis, delirium, or were prescribed >1 antipsychotic.

The primary outcome measure was the average titration rate of the newly initiated antipsychotic, defined as the average number of days it took for a scheduled antipsychotic dose increase of any size to occur. Secondary outcome measures included differences in the primary outcome between patients admitted involuntarily versus voluntarily, the prevalence of individuals titrated to the guideline-recommended maximum dose prior to discharge, time between starting and final dose, and whether an LAI was initiated prior to discharge. These outcomes were measured to allow for more comprehensive analysis of antipsychotic use patterns in the inpatient setting. For example, it is important to understand dosing patterns in addition to titration strategies and whether these practices differ based on a patient's willingness to engage in treatment. Guideline-recommended maximum doses were defined using dosing recommendations from the World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Schizophrenia.[15] These guidelines were used because they provide dose ranges for all first- and second-generation antipsychotics commonly used at BUMCS. Data was also collected on adjunct mood stabilizer use and total number of psychotropics to capture patients' perceived severity of illness because no other measures for this were available.

Descriptive statistics were used to describe demographic information and clinical characteristics. A Shapiro-Wilk test was used to determine parametric assumptions, and a Wilcoxon rank sum test was used to determine differences in titration rate between patients admitted involuntarily versus voluntarily. The University of Arizona Institutional Review Board approved the study protocol prior to evaluation of patient data.

Results

A total of 149 patients were included after screening for inclusion/exclusion criteria (Figure). Demographics and clinical characteristics are reported in Table 1. The

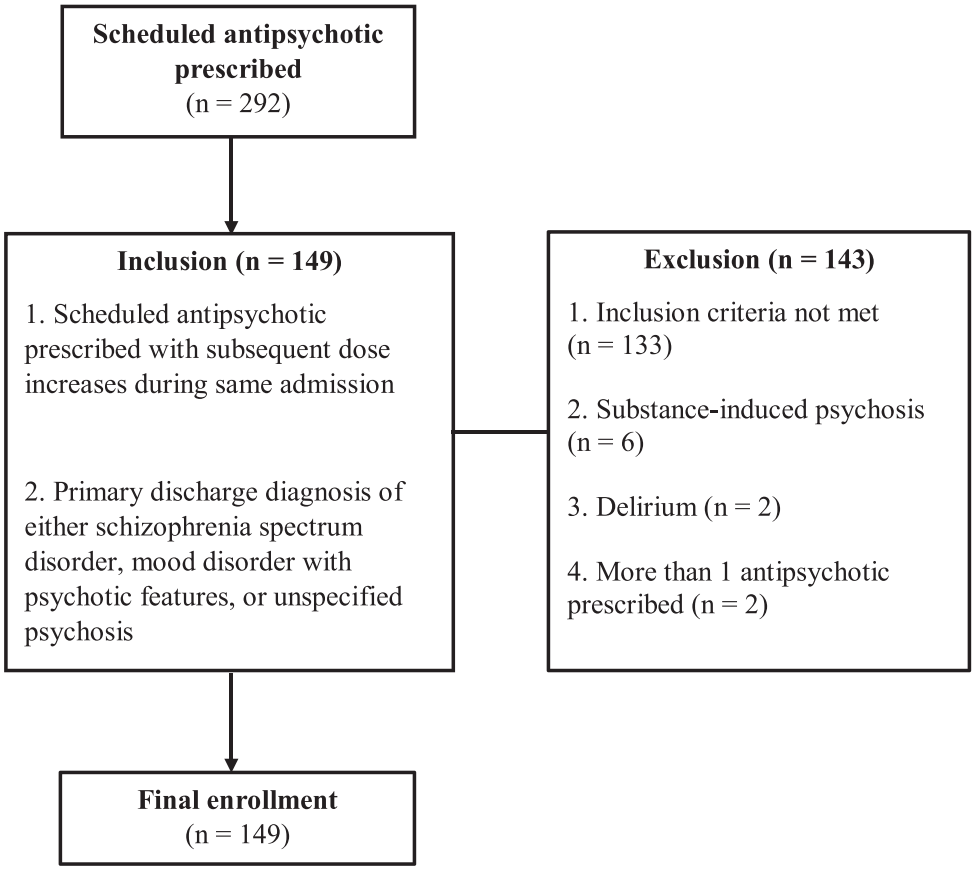

FIGURE: Patient enrollment information

majority of patients were male (69.1%) and were admitted involuntarily (66.4%). The most common primary diagnosis documented on discharge was schizophrenia spectrum disorder (61.1%) followed by bipolar disorder with psychotic features (24.8%) and unspecified psychosis (14.1%).

TABLE 1: Demographic and baseline characteristics of the study (N = 149)[a]

Characteristic	Value
Age, median (IQR)	37 (27 to 52)
Male sex	103 (69.1)
Ethnicity	
White	73 (49.0)
African American	14 (9.4)
Hispanic	39 (26.2)
Other	19 (12.8)
Unknown	4 (2.7)
Involuntary admission	99 (66.4)
Primary discharge diagnosis	
Schizophrenia spectrum disorder	91 (61.1)
Bipolar disorder with psychotic features	37 (24.8)
Psychosis unspecified	21 (14.1)

IQR = interquartile range.

[a]In n (%) format unless otherwise noted.

Antipsychotics were titrated on average every 2 days (Table 2). It took an average of 3 days for patients to be titrated from their starting dose to the final dose during hospitalization. There was no difference in titration rate between patients admitted involuntarily versus voluntarily (involuntary: 2, interquartile range: 1, 2.5 vs voluntary: 1.8, interquartile range: 1, 3; $P = .96$). The percentage of patients who were titrated to the guideline-recommended maximum dose was 18.1%, and 31.5% of patients were transitioned to an LAI. The average length of stay was 9 days, and 43.6% of patients were readmitted within 1 year.

The frequencies of different antipsychotics prescribed are provided in Table 2. Risperidone was most commonly prescribed (24.2%), followed by paliperidone (20.1%), olanzapine (14.8%), quetiapine (13.4%), and aripiprazole (12.8%); 38.9% of patients were prescribed an adjunct mood stabilizer, and patients had an average of 2 psychotropic medications prescribed in total. Only 4.1% of patients had a documented adverse effect although 84.9% of patients did not have any documentation provided regarding adverse effects. Of the 6 patient

TABLE 2: Clinical characteristics and study outcomes (N = 149)[a]

Study Information	Value
Antipsychotic initiated	
Aripiprazole	19 (12.8)
Chlorpromazine	1 (0.7)
Clozapine	9 (6.0)
Fluphenazine	6 (4.0)
Haloperidol	5 (3.4)
Lurasidone	1 (0.7)
Olanzapine	22 (14.8)
Paliperidone	30 (20.1)
Quetiapine	20 (13.4)
Risperidone	36 (24.2)
Time to antipsychotic dose increase in days, median (IQR)	2 (1 to 3)
Time from start to final dose in days, median (IQR)	3 (2 to 6)
Titrated to guideline recommended max dose	27 (18)
Transitioned to long-acting injectable	47 (31.5)
Adjunct mood stabilizer[b]	58 (38.9)
Total No. psychotropics, median (IQR)[c]	2 (1 to 2)
Length of stay in days, median (IQR)	9 (6 to 14)
Readmitted in past year	65 (43.6)

IQR = interquartile range.

[a]In n (%) format unless otherwise noted.

[b]Defined as being prescribed scheduled lithium, divalproex sodium, carbamazepine, or oxcarbazepine.

[c]Defined as any scheduled medication used for the treatment of psychiatric symptoms; determined by documented discharge medication list provided in discharge summary.

encounters with documented adverse effects, 2 were reported as akathisia, 1 as oral-buccal involuntary movements, 1 as leg cramps, and 2 as EPS (without specifying the type of EPS). Antipsychotic dosing characteristics are provided in Table 3.

Discussion

This study demonstrates that antipsychotics are titrated very quickly in the inpatient setting with almost 1 in 5 patients being titrated to maximum dosages within 3 days on average.[2] Interestingly, despite the rationale that antipsychotics must be titrated quickly in the acute care setting to help patients recover faster and discharge sooner, the average length of stay was 3 times higher than the average time it took for patients to be titrated to their final treatment dose, and almost half of patients were readmitted within 1 year.

Although guidelines for acute treatment recommend medications be titrated quickly to a therapeutic dose,[2,15] there are no specific recommendations on what titration rate is optimal for achieving rapid response while minimizing adverse effects. Additionally, dose requirements vary between patients, making it difficult to know an individual's target therapeutic dose ahead of time. Once an antipsychotic is titrated to the lower end of the recommended dosing range, it becomes unclear how much additional benefit will come from increasing the dose further. In fact, a previous randomized controlled trial[16] in 2016 found that among 103 patients with schizophrenia who failed to respond to moderate doses of olanzapine or risperidone, increasing the dose further did not result in significant improvements in response rate. Additionally, the study completion rate was significantly higher in the continuation group compared to the dose increment group, demonstrating that patients who continued to have their dose increased were less likely to adhere to treatment.

The majority of patients included in our study had a documented diagnosis of schizophrenia. Treatment nonadherence rates in this population range from 26.5% to 68.8%,[17] which is significant because this increases the

TABLE 3: Antipsychotic dosing patterns, mg[a]

Antipsychotic	Starting Dose, Median (IQR)	Final Dose, Median (IQR)	Final Dose, Chlorpromazine Equivalents
Aripiprazole	5 (5 to 10)	20 (12.5 to 20)	267
Chlorpromazine[b]	200	400	400
Clozapine	25 (25 to 25)	300 (200 to 350)	300
Fluphenazine	10 (5 to 10)	20 (10 to 20)	1000
Haloperidol	5 (2 to 10)	15 (10 to 15)	750
Lurasidone[b]	20	60	375
Olanzapine	10 (5 to 10)	15 (10 to 15)	300
Paliperidone	6 (3 to 6)	9 (9 to 12)	450
Quetiapine	100 (100 to 200)	300 (200 to 400)	400
Risperidone	2 (1 to 2)	4 (3 to 4)	400

IQR = interquartile range.

[a]Dose rounded to nearest strength availability.

[b]No interquartile range reported because N = 1.

risk of suicide, psychotic relapse, and hospital admission.[18] Recent evidence suggests that LAI antipsychotics reduce the risk of rehospitalization in patients with schizophrenia compared to oral antipsychotics[19,20]; therefore, these agents are often used at BUMCS in patients with a history of treatment nonadherence. This explains why the majority of patients in our sample were prescribed an oral antipsychotic with an LAI formulation available because prescribers may prefer to have this as a treatment option (Table 2). Before an LAI is administered, it is recommended that the patient be trialed on the oral formulation first to establish tolerability and efficacy.[21] However, there are no specific recommendations on how long this oral trial should last. As a result, prescribers may limit this trial to just a few days to rule out acute dystonic reactions even though other types of adverse effects (eg, akathisia, pseudoparkinsonism) may occur weeks to months later.[22,23] Additionally, this is often not enough time to determine how efficacious the antipsychotic will be because it can take weeks for patients to respond to treatment.[2,10] Patients may, therefore, be initiated on an LAI quickly only to have minimal improvement in their symptoms and later become rehospitalized.

Because previous studies[24,25] show that involuntary patients may be at greater risk of being prescribed high antipsychotic doses, we compared titration rates between patients that were admitted to BUMCS involuntarily versus voluntarily. It was hypothesized that patients admitted involuntarily might have their doses titrated more rapidly because they can initially refuse treatment for days prior to a court order being issued. However, both groups had antipsychotic doses titrated on average every 2 days, demonstrating that this titration rate is common regardless of voluntary treatment status. Although objective data was not available regarding patients' severity of illness, most patients admitted to BUMCS are determined to be a DTS/DTO or PAD due to decompensation of a severe mental illness. Because BUMCS is a level 1 inpatient facility, the goal of hospitalization is to quickly stabilize patients, so they are no longer a DTS/DTO or PAD. This likely puts pressure on prescribers to titrate antipsychotics quickly with the hopes of reducing length of stay and hospitalization costs.

Although the goal of rapid antipsychotic titration in the acute care setting is to improve symptoms rapidly and reduce length of stay, it is unclear to what extent titration rate impacts either of these outcomes. A previous meta-analysis[26] found that rapid antipsychotic initiation was significantly superior to slow initiation for symptom improvement in schizophrenia in acute patient studies with no differences in tolerability. However, this study had several limitations, such as only 5 small acute patient studies being included with only 2 having been conducted in a double-blind fashion. Additionally, there were variations in antipsychotic titration strategies among the studies, and length of stay was not evaluated as an outcome. Our study found that the median length of stay was 3 times higher than the average time it took for patients to be titrated to their final antipsychotic dose. This may be reflective of situations in which a patient's symptoms warranting hospitalization have resolved, but issues related to transitions of care prevent them from being discharged.[27] Unfortunately, there is no marker in the medical record that indicates when a patient has stabilized from a psychiatric standpoint. Rather, this is something that is discussed daily between treatment team members because the patient's clinical condition can change while securing a disposition location.

Since the 1960s, there has been a large push for patients in psychiatric hospitals to be discharged as quickly as possible.[28] A Cochrane review[29] from 2014 evaluating length of hospitalization for people with severe mental illness concluded that short-stay policies do not lead to more readmissions, but that more large, well-designed trials are needed. This review[29] only includes 6 randomized controlled trials, all conducted between 1969 and 1980. Later studies[30-34] not included in the Cochrane review report that shortening psychiatric hospital stays leads to worse patient outcomes, such as increases in suicide and criminal acts and increases in acute readmission rates. Despite the mixed evidence, almost all Western countries in the past 50 years have shifted to a policy of reducing hospital lengths of stay.[35] This is because it is well known that reducing hospital stays significantly reduces the cost of health care expenditures associated with psychiatric treatment[36] even if the impact on clinical outcomes for patients with severe mental illness remains unclear.

The pressure to minimize length of stay may partially contribute to rapid antipsychotic titrations. Yet there is also a lack of evidence on how rapid dose titrations impact clinical outcomes. Future studies should investigate whether there is an association between antipsychotic dosing/titration patterns and nonadherence due to inefficacy or adverse effects. This is crucial given that antipsychotics can take weeks to months to take full effect, and certain adverse effects (eg, akathisia, pseudoparkinsonism) can also take this long to develop.

Limitations to this study are largely inherent to its retrospective design. For example, adverse effects were often not documented in the medical record; therefore, there was not a reliable way to obtain this information. Adverse effects may have developed following discharge; however, this could not be determined because it was not possible to obtain records from non-Banner outpatient facilities. Having access to these records would have allowed for further analysis to determine whether there is

an association between antipsychotic titration patterns and adverse effects or nonadherence. Data regarding severity of illness was also not available because this was not consistently documented in the medical record. In addition, information regarding treatment response during antipsychotic dose titration is only available via subjective documentation (objective rating scales are not used to track treatment response). Dosing information was based on the scheduled antipsychotic ordered and did not include additional doses that may have been administered as needed. Lastly, because we included patients without a documented diagnosis of schizophrenia but used dosing recommendations from schizophrenia practice guidelines, it is possible we underestimated the percentage of patients that were titrated to guideline-recommended maximum doses because some antipsychotics (eg, quetiapine) have lower dose recommendations in bipolar disorder versus schizophrenia.

Conclusion

Antipsychotics are titrated rapidly in the inpatient setting, often to guideline-recommended maximum doses. At our facility, antipsychotic titration rate did not differ between patients admitted voluntarily versus involuntarily, and about one-third of patients received an LAI prior to discharge. Further studies comparing slower versus faster titration strategies are needed to elucidate the impact of this on clinical outcomes although this may be logistically difficult in the current culture of inpatient psychiatry in which payers encourage shorter lengths of stay.

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