RAPID VERSUS STANDARD CLOZAPINE TITRATION ORDERS IN A PSYCHIATRIC ACUTE INPATIENT FACILITY

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Abstract
Objective: The aim of this study is to evaluate if rapid versus standard clozapine titration is associated with reduced length of stay (LOS) for treatment resistant psychiatric inpatients.
Methods: This retrospective chart review study collected socio-demographics and clinical outcomes of psychiatric inpatients with clozapine order sets, including primary diagnosis, order initiation date, discharge readiness and post-discharge placement. An electronic health record report of psychiatric inpatients with clozapine orders between September 2016 and April 2018 yielded 93 separate admissions receiving either rapid titration protocol (RTP) or standard titration (STP) based upon the physician preference.
Results: Of the 93 patients who were prescribed clozapine, 37 were started on the RTP and 56 were on the STP. The primary diagnosis of patients in both RTP and STP groups was Schizoaffective disorder at 78.38% and 62.5%, respectively. The median discharge ready (DCR) days were in fact lower for RTP than STP inpatients, although this was not statistically significant.
Conclusion: Ultimately, it was determined that the median LOS was similar between patients on rapid and standard titrations.

Key Words: Clozapine**,** refractory schizophrenia, rapid titration, standard titration

Introduction
Clozapine is a second generation or atypical antipsychotic medication that was approved by the FDA in 1989 for treatment of patients with refractory schizophrenia and bipolar disorder. It remains one of the most efficacious drugs for treatment-resistant schizophrenia.[1] It is however, associated with a variety of side effects, ranging from sedation and weight gain to seizures, agranulocytosis and myocarditis. Standard titration protocols, which are based on manufacturer's recommendation and clinical guidelines, suggest starting with 12.5-25 mg/day and increasing by 25 mg/day increments for the first week and 25-50 mg/day increases for week 2-3. This leads to a long delay of 2-3 weeks until patients are on the required dose, which can prolong time to symptom control and time to discharge readiness.[2] The longer titration protocol has been implemented to decrease risk of hypotension and cardiac side effects.

There are few reports examining rapid titration of clozapine and dosing regimens have differed. One study started titration at 25–50 mg followed by 50–100 mg as needed every 6 h on day 1, followed by increases of 50–100 mg/day, while another described a rapid titration protocol (RTP) where patients received 612.5 mg or 812 mg in the first 9 days.[3,4] Currently, there are three published research accounts of clozapine RTPs: Two describe outcomes with treatment refractory schizophrenia, and the third addresses treatment refractory bipolar disorder.[2,3,5] All three conclude that rapid clozapine titration appeared to be safe and effective for treatment-refractory schizophrenia. There were no recorded published reports of rapid titration protocols in the United States.

In 2016, the Valleywise Psychiatry Department added an RTP order set to the existing standard titration order available to clinicians. Standard titration at Valleywise starts at 12.5mg/day with the dose gradually increasing to 300mg by day 14. Rapid/accelerated titration reaches 300mg by day 10, and 450 mg by day 14. Documenting the duration timing of rapid versus standard titration was a way to better understand the effect on hospitalization length of stay (LOS) that may lead to decreased overall healthcare costs.

Additionally, these outcome may confirm the value of rapid titration for treating the severely mentally ill in public safety net hospitals. As the literature currently summarizes, clozapine, a relatively inexpensive treatment, is often underutilized by clinicians, because of the extensive monitoring requirements and risk of side effects, despite its proven effectiveness for symptom control.

In this study, we compare rapid versus standard clozapine titration and its association with length of stay (LOS) for treatment resistant psychiatric inpatients. We hypothesized that both protocols are equally

effective and safe, but that patients treated with the rapid titration method will require fewer days until they are ready for discharge.

Methods

Setting

The patients described in the study were admitted to Valleywise inpatient psychiatric units between September 2016 and April 2018. A total of 93 separate admissions receiving either rapid titration protocol (RTP) or standard titration (STP) were yielded.

Patient Population

This Valleywise Health Institutional Review Board (IRB) approved retrospective cohort chart review study collected socio-demographic data and clinical outcomes of psychiatric inpatients with clozapine order sets, including primary diagnosis, order initiation date, discharge readiness and post-discharge placement. Only adult psychiatric inpatients aged 18 or older at admission and initiating clozapine treatment at Valleywise after admission and (treatment refractory) diagnosis of schizophrenia or schizoaffective disorder were included in the final sample for analysis.

Clozapine administration protocol

Patients on maintenance dosage or whose orders were altered or stopped upon initiation of orders were excluded. Standard titration at Valleywise normally starts at 12.5mg/day with the dose gradually increasing to 300mg by day 14. Rapid/accelerated titration reaches 300mg by day 10, and 450 mg by day 14. Patients received either rapid titration protocol (RTP) or standard titration (STP) based upon the physician preference. Patients on RTP were compared to those on STP for overall length of stay (LOS) and time from admit to 'discharge ready' (DCR) status. DCR was analyzed in order to account for those stable enough for release but whose discharge date may be delayed due to lack of a discharge placement in the community. An additional variable of time from treatment initiation date to DCR date was also evaluated.

Statistical Analysis

Demographic/clinical characteristics and duration of stay of patients treated with the standard and rapid clozapine titration protocols were compared using the Mann–Whitney U test (Wilcoxon rank-sum with continuity correction). The primary outcome was the overall LOS in each group. Secondary outcomes included discharge ready (DCR) status, primary diagnosis of patients, and post-discharge placement.

Results

Demographic and Clinical Characteristics

There were 60 male and 33 female subjects in our sample, identifying racially as White (72), African American (12), Native American/Alaskan (5), and Asian/Pacific Islander (4). Fourteen percent claimed Hispanic ethnicity. The primary diagnosis of patients in both RTP and STP groups was Schizoaffective disorder at 78.38% and 62.5%, respectively. In terms of post-discharge placement, 24.32% of RTP

patients went to a 24 hr residential and 18.19% to home. In the STP group, 25% went to a 24 hr residential and 30.36% were discharged home.

Table 1. Rapid Titration Recipients

DX Class	Principal Diagnosis MDP Note	Frequency Count	Dx Class count	Percent of Total Frequency
1 – Schizophrenia & Psychotic disorders	Schizoaffective	29	36	97%
	Schizophrenia	6		
	Disorganized Schizophrenia	1		
3 – Bipolar	Bipolar	1	1	3%
6 – Personality Disorder	None	0		
Total			37	100%

Table 2. Standard Titration Recipients

DX Class	Principal Diagnosis MDP Note	Frequency Count	Dx Class count	Percent of Total Frequency
1 – Schizophrenia & Psychotic disorders	Schizoaffective	35	52	93%
	Schizophrenia	15		
	Disorganized / Undifferentiated Schizophrenia	2		
3 – Bipolar	Bipolar & Bipolar I	3	3	5%
6 – Personality Disorder	Borderline PD	1	1	2%
Total			56	100%

Clozapine titration time and effect on LOS and DCR

The mean and median LOS for patients on the RTP (n = 37) was 120.43 and 81 days, while that for STP patients (n=56) was 111.98 and 81.5 days, (p=0.866). When measured in terms of days to being discharge ready, RTP subjects had mean and median stays of 93.38 days and 51.5 days, as compared to STP subject mean and median stays of 93.28 days and 76.5 days, (p=0.644). Minimum and maximum values for both RTP and STP group DCR days (13 to 366, and 18 to 404 days), reveal a significant number of outliers. The mean and median time from Clozapine initiation date to discharge ready date for patients on RTP was 70.79 and 31.5 days, while that of patients on STP was 71 and 36 days (p=0.559).

Table 3. Results Summary

	N	Mean	Median	Min	Max	P
Total LOS	93	115.52	81	12	481	
Discharge ready LOS	64	93.31	72.5	13	404	
Admit Age	93	38.82	37	18	66	
Admit date to Clozapine initiation	93	28.86	13	0	370	
Clozapine initiation date to discharge ready date	63	70.92	36	8	385	
Accelerated titration						
	N	Mean	Median	Min	Max	
Total LOS	37	120.86	81	12	447	0.866
Discharge ready LOS	24	93.38	51.5	13	366	0.644
Admit Age	37	38.27	37	18	66	0.745
Admit date to Clozapine initiation	37	22.54	13	1	97	0.608
Clozapine initiation date to discharge ready date	24	70.79	31.5	8	331	0.559
Standard titration						
	N	Mean	Median	Min	Max	
Total LOS	56	111.98	81.5	17	481	
Discharge ready LOS	40	93.28	76.5	18	404	
Admit Age	56	39.18	36.5	18	66	
Admit date to Clozapine initiation	56	33.04	15.5	0	370	
Clozapine initiation date to discharge ready date	39	71	36	13	385	

*P value comparing accelerated vs standard titration, Wilcoxon rank sum two tailed P, with t-approximation

Discussion

The purpose of this retrospective study was to compare rapid versus standard clozapine titration and potential association with reduced length of stay (LOS) for treatment resistant psychiatric inpatients. Previous literature was reviewed and highlighted that rapid titration dosing regimen of clozapine is safe and efficacious. [2,3,5] However, studies are limited with no documented reports in the United States. Additional considerations include the tolerability of individuals to the rapid versus standard titration and discontinuation if severe side effects were experienced. [2] In our patient population, standard titration

normally started at 12.5 mg/day with the dose gradually increasing to 300 mg by day 14. Rapid/accelerated titration typically reached 300 mg by day 10, and 450 mg by day 14.

A shorter LOS among those on RTP was anticipated by the fact that RTP allows a minimally effective therapeutic dose range to be reached sooner than standard titration, hence presuming quicker stabilization. In this study, median LOS was essentially similar between patients on rapid and standard titrations, (81 to 81.5 days, P = 0.866). Median discharge ready (DCR) days were in fact lower for RTP than STP inpatients (51.5 to 76.5 days, p=0.644), although this was not statistically significant. Importantly, minimum and maximum values for both RTP and STP group DCR days (13 to 366, and 18 to 404 days), reveal a significant number of outliers. Any expected difference in LOS may be offset by clinical and system-level factors of which we only peripherally accounted for. One important impact on DCR values could be due to inconsistent documentation. This study has several limitations including small sample size and incomplete account of cofactors including comorbidities contributing to extended DCR. Future studies with a larger sample of patients and consistent DRS recording would improve the accuracy of results. Additionally, there continues to be a need for large, randomized, double blinded clinical trials to further assess the efficacy of rapid clozapine titration versus standard titration.

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None.

Conflict of Interest

Bhupinder Kaur has declared no conflicts of interest
Shabnam Sood has declared no conflicts of interest
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None.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Valleywise Health Institutional Review Board) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was not obtained from individual subjects whose information is included in the study as it was a chart review protocol receiving a HIPAA Waiver of Authorization and a Waiver of Informed Consent by the Institutional Review Board of record.

References

1. McEvoy J. Effectiveness of Clozapine Versus Olanzapine, Quetiapine, and Risperidone in Patients With Chronic Schizophrenia Who Did Not Respond to Prior Atypical Antipsychotic Treatment. *Am J Psychiatry*. 2006;163(4):600. doi:10.1176/appi.ajp.163.4.600
2. Poyraz CA, Özdemir A, Sağlam NGU, et al. Rapid Clozapine Titration in Patients with Treatment Refractory Schizophrenia. *Psychiatr Q*. 2016;87(2):315-322. doi:10.1007/s11126-015-9394-y
3. Ifteni P, Correll CU, Nielsen J, Burtea V, Kane JM, Manu P. Rapid clozapine titration in

treatment-refractory bipolar disorder. *J Affect Disord*. 2014;166:168-172. doi:10.1016/j.jad.2014.04.020

4. Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, Wolfe R, McNeil JJ. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: A case-control study. *Schizophr Res*. 2012;141(2-3):173-178. doi:10.1016/j.schres.2012.08.018
5. Ifteni P, Nielsen J, Burtea V, Correll CU, Kane JM, Manu P. Effectiveness and safety of rapid clozapine titration in schizophrenia. *Acta Psychiatr Scand*. 2014;130(1):25-29. doi:10.1111/acps.12241