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Comparison of clozapine doses and tolerability in patients with and without concurrent valproic acid

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Abstract

Introduction: Valproic acid (VPA) and its various formulations can be given in conjunction with clozapine for seizure prophylaxis or for augmentation in schizophrenia. There is conflicting literature on how VPA affects clozapine metabolism and the incidence of clozapine-related side effects. The purpose of this study is to compare the effects of VPA when given concurrently with clozapine to patients on clozapine monotherapy.

Methods: A retrospective medical record review was completed to identify patients admitted to the inpatient psychiatry unit at an academic medical center with an order for clozapine with and without concurrent VPA from August 7, 2010 to August 7, 2020. The primary outcome was the difference in clozapine doses in patients on clozapine as monotherapy versus dual therapy with VPA. Secondary outcomes include the difference in incidence of adverse effects in monotherapy versus dual therapy, as well as clozapine and norclozapine concentrations in both treatment groups.

Results: During the study period, 73 patients were included in the monotherapy group and 35 patients were included in the dual therapy group. The average clozapine dose in the dual therapy group was 250 mg (95% CI = 194.7, 305.4) which was significantly higher than the average monotherapy dose of 175.9 mg (95% CI = 134.0, 208.7; $P = .016$). However, there was no significant difference in the average clozapine concentration between the dual therapy group (392.5 ng/mL; 95% CI = 252.8, 532.2) and monotherapy group (365.9 ng/mL; 95% CI = 260.5, 471.3; $P = .756$). There were higher rates of tachycardia (45.7% vs 17.8%; $P = .002$), sedation (51.4% vs 8.2%; $P < .001$), and constipation (42.8% vs 9.5%; $P < .001$) in the dual therapy group compared to the monotherapy group, respectively.

Discussion: Patients on concurrent clozapine and VPA received higher doses of clozapine and experienced a higher incidence of tachycardia, sedation, and constipation.

Keywords: clozapine, norclozapine, valproic acid, divalproex, schizophrenia, pharmacokinetics, drug interactions

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Introduction

Clozapine is an effective antipsychotic for the treatment of schizophrenia and schizoaffective disorder, however, its

place in therapy is reserved for a third-line option because of its relatively high risk of serious adverse events compared to other antipsychotics. Associated adverse effects include metabolic abnormalities, seizures, orthostatic hypotension, myocarditis, and severe neutropenia that requires a Risk Evaluation Mitigation Strategy program.[1] Clozapine dosing varies, but the average effective clozapine dose has been suggested to be 200 to 600 mg/d.[2] Given the wide dose range, clozapine concentrations are often used to guide titration, with the average effective concentration being 200 to 550 μg/L.[3]

Valproic acid (VPA) can be used as an augmenting agent in combination with clozapine for schizophrenia. It can also be used for seizure prophylaxis due to increased incidence of seizures with higher clozapine doses. Incidence of seizures with clozapine is dose-dependent and is reported in one study to be 0.6% to 2% in doses <300 mg, 1.8% to 4% in doses of 300 to 599 mg, and 5% to 14% in doses of 600 to 900 mg.[4]

Limited publications[5-7] suggest patients require higher dosages of clozapine with the addition of VPA. Conversely, one study[7] suggests that VPA increases the incidence of clozapine-related side effects, requiring a decrease in daily clozapine dose. A retrospective study[8] of 49 patients compared patients on VPA or lithium in addition to clozapine versus clozapine monotherapy and found rates of sedation, tachycardia, gastrointestinal disturbances, confusion, and dizziness were similar in all 3 groups. Therefore, this study aims to explore this relationship further by comparing the effects of VPA when given concurrently with clozapine to patients on clozapine monotherapy, including measuring any differences in clozapine dosing, concentrations, or adverse effects. The secondary outcome of this study was to compare any differences in clinical outcomes between the 2 study groups by comparing hospital length of stay.

Methods

Settings and Participants

A retrospective electronic medical record review was completed for patients admitted to the inpatient psychiatric unit from August 7, 2010 to August 7, 2020. The study was approved by the IRB. A list of patients was generated using Cerner Information Systems for those who received clozapine orders while inpatient, with and without VPA.

Inclusion criteria included all patients with a clozapine order during their first psychiatric admission within the study period. Exclusion criteria consisted of patients <18 years old, pregnant patients, incarcerated patients, and subsequent admissions beyond a patient's first admission. Encounters were included if a patient had an inpatient admission with clozapine monotherapy and a subsequent admission on dual therapy with VPA, or vice versa, to avoid skewing data toward patients with multiple admissions on clozapine. Patients who received clozapine and VPA (including all of its formulations) during the admission were included in the dual therapy group. Patients who received clozapine without any VPA order during admission were included in the monotherapy group.

Data Collection

Baseline characteristics collected included patient age, sex, race, ethnicity, BMI, and smoking status. Smoking status was grouped into nonsmoker, smoking <10 cigarettes per day, or smoking >10 cigarettes per day. Smoking status was used as a marker to estimate if cytochrome P450 (*CYP*)*1A2* induction may have impacted clozapine metabolism during admission, as smoking over 10 to 15 cigarettes per day can significantly induce *CYP1A2*.[9] Concurrent psychiatric medications that patients received during admission along with the study drugs were recorded. Concurrent moderate *CYP1A2* or *CYP3A4* inhibitors or inducers were recorded based off the list from the US FDA Center for Drug Evaluation.[10] Adverse effects were noted during inpatient admission through a medical record search with predefined terms to encompass constipation, hypotension, myocarditis, neutropenia, sedation, sialorrhea, tachycardia, and clozapine-induced seizures, and their incidence were recorded. Dosages of clozapine and VPA, as well as clozapine and norclozapine concentrations, were recorded and a mean dose or concentration were calculated throughout inpatient admission.

Statistical Analysis

All data was recorded in REDCap. All data analysis was performed on IBM SPSS Statistics for Windows (version 27.0). Baseline weight and age, mean dosing, concentrations, and length of stay were compared with 2-tailed unpaired *t* tests with a significance concentration of 0.05. Baseline characteristics and adverse effect incidence was compared with 2-tailed χ^2 tests with a significance concentration of 0.05.

Results

During the study period, 73 patients were included in the clozapine monotherapy group and 35 patients in the clozapine and VPA dual therapy group (Table 1). No patients met criteria for exclusion. The mean age of the monotherapy group and dual therapy group was 43.8 and 46.1 years old, respectively. Regarding sex, 49.3% of monotherapy and 54.3% of dual therapy patients were female at birth. There was a lower percentage of White

TABLE 1: Baseline characteristics of the study

Characteristic	Monotherapy, n (%) n = 73	Dual Therapy, n (%) n = 35	*P* Value
Mean age, y (95% CI)	43.8 (39.8, 47.4)	46.1 (41.3, 50.9)	.296
Female at birth	36 (49.3)	19 (54.3)	.629
White	36 (49.3)	23 (65.7)	.109
African American	29 (39.7)	11 (31.4)	.403
Mean weight, kg (95% CI)	90.85 (83.37, 98.33)	86.51 (78.71, 94.32)	.474
Concurrent scheduled antipsychotic for switching to clozapine	37 (50.7)	19 (54.3)	.726
Concurrent scheduled antipsychotic for multiple antipsychotic regimen	15 (20.5)	6 (17.1)	.676
Concurrent antidepressant	27 (37.0)	12 (34.3)	.784
Concurrent CYP1A2/3A4 inhibitor[a]	5 (6.8)	1 (2.9)	.397
Ciprofloxacin	2 (2.7)	0 (0)	.323
Fluconazole	1 (1.4)	0 (0)	.826
Fluvoxamine	2 (2.7)	1 (2.9)	.954
Concurrent CYP1A2/3A4 inducer[a]	15 (20.5)	12 (34.3)	.240
Carbamazepine	2 (2.7)	1 (2.9)	.972
Oxcarbazepine	1 (1.4)	1 (2.9)	.592
Armodafinil	1 (1.4)	0 (0)	.826
Phenytoin	1 (1.4)	0 (0)	.826
Smoking >10 cigarettes/d	10 (13.7)	10 (28.6)	.063

[a]Concurrent *CYP1A2* and *CYP3A4* inhibitors and inducers were screened based off FDA classification.[10]

patients in the monotherapy group (49.3%) compared to the dual therapy group (65.7%). There was a higher percentage of African American patients in the monotherapy group (39.7%) compared to the dual therapy group (31.4%). The majority of patients were on other concurrent psychotropic medications, with 97.2% of patients in the monotherapy group and 97.1% of patients in the dual therapy group. In the monotherapy group, 37 patients (50.6%) were on concurrent antipsychotics with the intention to switch to clozapine as monotherapy, compared to 19 patients (54.2%) in the dual therapy group. In comparison, 15 patients (20.5%) in the monotherapy group were on concurrent antipsychotics with the intention of stabilizing on a multiple antipsychotic regimen, compared to 6 patients (17.1%) in the dual therapy group.

There was minimal difference in the incidence of concurrent *CYP1A2* or *CYP3A4* inhibitors in the monotherapy or dual therapy groups; however, 34.2% of patients in the dual therapy group had concurrent *CYP1A2/CYP3A4* induction compared to 17.8% in monotherapy group (Table 1). The majority of *CYP1A2* induction in both groups was made of patients who smoked more than 10 cigarettes per day prior to their admission.

The average clozapine dose, defined as the average dose over the length of days admitted and taking clozapine, was 250 mg in the dual therapy group, which was significantly higher than the average clozapine dose in the monotherapy group of 175.9 mg ($P = .016$; Table 2). There was no significant difference in length of stay between the 2 groups (Table 2).

Clozapine serum concentrations were obtained during admission in 21 (28.8%) clozapine monotherapy patients, and 10 (28.6%) of the patients on dual therapy. The average clozapine concentration in the dual therapy group was 392.5 ng/mL, which was not significantly different from the average clozapine concentration in the monotherapy group of 365.9 ng/mL ($P = .756$; Table 3).

The incidence of any adverse effect in the dual therapy group was 74.2%, as compared to 38.3% in the monotherapy group ($P < .001$; Table 2). Rates of constipation, sedation, and tachycardia were significantly higher in the dual therapy group compared to the monotherapy group. Rates of sedation and sialorrhea were similar in both groups. One patient in each group had neutropenia while on clozapine, requiring an interruption of therapy while admitted. No patients in either group experienced clozapine-induced myocarditis. In the dual therapy group, 4 patients (11.4%) had VPA added specifically for seizure prophylaxis because of clozapine, whereas the other patients had VPA added for other indications. In the dual therapy group, no patients discontinued clozapine because of an adverse effect, compared to 5 patients (6.8%) in the monotherapy group: 3 patients discontinued clozapine because of tachycardia, and 2 patients discontinued because of hypotension. When comparing the incidence of adverse effects in patients with

TABLE 2: Comparison of clozapine outcomes and adverse effects

Result	Monotherapy, n (%) n = 73	Dual Therapy, n (%) n = 35	*P* Value
Mean clozapine dose, mg (95% CI)	175.9 (134, 208.7)	250.0 (194.7, 305.4)	.016
Highest mean clozapine dose, mg (95% CI)	239.6 (204.3, 274.8)	327.0 (269.1, 385.1)	.008
Length of stay, d (95% CI)	19.78 (14, 25.5)	19.9 (13, 26.7)	.978
Any adverse effect	28 (38.4)	26 (74.3)	<.001
Tachycardia	13 (17.8)	16 (45.7)	.002
Hypotension	13 (17.8)	7 (20.0)	.784
Sedation	6 (8.2)	18 (51.4)	<.001
Sialorrhea	10 (13.7)	8 (22.9)	.232
Constipation	7 (9.6)	15 (42.9)	<.001
Neutropenia	1 (1.4)	1 (2.9)	.592
Myocarditis	0	0	. . .
Seizures	1 (1.4)	0	.826
VPA added for seizure prophylaxis	. . .	4 (11.4)	. . .
Clozapine discontinued due to adverse effect	5 (6.8)	0 (0)	.113

VPA = valproic acid.

concurrent *CYP1A2/CYP3A4* inducers versus no inducers, there was a significantly higher incidence of tachycardia in the group with no inducers compared to the group with inducers (30.1% vs 12.0%; $P = .04$). There were no other significant differences in adverse effects between the groups with *CYP1A2/CYP3A4* inducers and with no inducers. In the monotherapy group, 1 patient had a seizure that was attributed in part to clozapine. The patient was on carbamazepine and clozapine when first admitted, but carbamazepine was discontinued and the clozapine dose was subsequently decreased. The patient was started on VPA after experiencing a seizure while on clozapine monotherapy following carbamazepine discontinuation. The patient had a prior history of seizures and had previously been treated with topiramate and carbamazepine.

Discussion

In this retrospective medical record review of patients on clozapine monotherapy versus dual therapy with concurrent VPA, our findings suggest dual therapy patients receive higher dosages of clozapine. One possibility for this finding is that higher dosages required in the dual therapy group may suggest that dual therapy patients were more symptomatic than the monotherapy group and required higher clozapine dosages. Another consideration is the difference in *CYP1A2* inducers in the dual therapy group compared to the monotherapy group may have contributed the need for higher dosages in the dual therapy group to obtain similar drug concentrations. It should be noted that the majority of patients in the study did not have clozapine concentrations drawn during their admission, and thus any conclusions regarding clozapine concentrations and its relation to clozapine doses and related side effects are limited. Of note, the psychotropic effects of VPA were the primary reason for use, rather than for seizure prophylaxis, suggesting a higher acuity of care necessary in dual therapy patients.

This study found that dual therapy patients experience significantly higher adverse event rates compared to monotherapy patients—specifically increased rates of constipation, sedation, and tachycardia. There are multiple possibilities for the differences in adverse effects. The higher incidence of these adverse effects could be dose-related effects of clozapine, although a sample of clozapine concentrations between both study groups were similar. An additional consideration is if the difference in adverse

TABLE 3: Comparison of drug concentrations

Result	Monotherapy With Drug Concentrations, ng/mL (95% CI) n = 21	Dual Therapy With Drug Concentrations, ng/mL (95% CI) n = 10	*P* Value
Mean clozapine	365.9 (260.5, 471.3)	392.5 (252.8, 532.2)	.756
Mean norclozapine	151.2 (111.8, 190.7)	147.8 (75.7, 219.8)	.830

effects may be related to an additive pharmacodynamic interaction between VPA and clozapine. VPA has its own inherent risk of tachycardia, sedation, and constipation, which, when combined with clozapine, may make patients more susceptible to experience these adverse effects. A recent study[11] of 288 patients on clozapine and concurrent VPA found dose-adjusted concentrations of clozapine were unchanged, whereas dose-adjusted concentrations of *N*-desmthylclozapine and clozapine N^+-glucuronide were reduced, and dose-adjusted concentrations of clozapine 5*N*-glucuronide were increased, suggesting that any pharmacokinetic interactions between clozapine and VPA involve clozapine metabolites rather than clozapine itself. This could potentially explain the difference in side effects between groups, despite a significant difference in doses but similar drug concentrations between groups, as these concentrations do not reflect other pertinent clozapine metabolites beyond norclozapine that still can significantly affect adverse effect incidence. Future studies are needed to explore the clinical significance of other clozapine metabolites on efficacy and side effects.

Multiple limitations of this study should be acknowledged. Given the small sample size of this study, the possibility that a type II error occurred when a nonsignificant difference was found should be acknowledged. Although diligence was taken to distinguish adverse effects due to clozapine, certain adverse effects (ie, sedation) are common among many psychotropic medications, which should be considered when developing conclusions from this study. Another limitation was the small percentage of included patients with clozapine and norclozapine concentrations. These concentrations were similar in both groups, although the difference in clozapine doses and small sample size of patients with concentrations limit what can be inferred from this finding.

Finally, this study primarily focused on *CYP1A2* and *CYP3A4*-mediated drug-drug interactions. Although *CYP2D6* and *CYP2C19* each are thought to be involved in 5% of clozapine metabolism,[12] there may still be relevant *CYP2D6* and *CYP2C19*-mediated drug-drug interactions that could affect clozapine or other concurrent psychotropic medications. This study found that there was a higher percentage of relevant *CYP1A2* and *CYP3A4* inducers in the dual therapy group compared to the monotherapy group. This may contribute to differences in dosing and adverse effects and should be considered a limitation of the study. The primary *CYP1A2* inducer prevalent in the dual therapy group was concurrent smoking of >10 cigarettes per day. Although patients are not exposed to tobacco during admission, the inducing effects of cigarette use may last days into their inpatient admission.[13] There were 8 patients (10.9%) in the monotherapy group who smoked <10 cigarettes per day, compared to 3 patients (8.6%) in the dual therapy group, which should be noted when considering partial enzyme induction of *CYP1A2*.

In conclusion, patients in this study on concurrent clozapine and VPA received higher dosages of clozapine and experienced a higher incidence of constipation, sedation, and tachycardia than those on clozapine monotherapy. These findings contradict a previous study[7] suggesting the rate of clozapine-related side effects were similar in clozapine monotherapy versus clozapine and VPA dual therapy groups. The increased dose of clozapine required in dual therapy groups are in line with previous studies,[4-6] suggestive of a significant induction effect from VPA requiring higher dosing of clozapine. A recent study[8] points to a pharmacokinetic interaction between VPA and clozapine metabolites being central in this interaction. There was no difference in length of stay between monotherapy and dual therapy groups. Although this study is limited in inferring some pharmacokinetic interactions because of the limited therapeutic drug monitoring, future studies with a larger sample size of patients with clozapine concentrations can explore the pharmacokinetic relationship with clozapine and VPA and its associated clinical outcomes.

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