Four cases of myocarditis in US hospitals possibly associated with clozapine poor metabolism and a comparison with prior published cases

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Objectives: Clozapine-induced myocarditis may be a hypersensitivity reaction due to titration that was too rapid for a patient's clozapine metabolism. Obesity, infections, and inhibitors (e.g., valproate) may lead to clozapine poor metabolizer (PM) status. The hypothesis that 4 patients with clozapine-induced myocarditis from two United States hospitals were clozapine PMs was tested by studying their minimum therapeutic clozapine doses and titrations. **Methods:** Using methodology from a prior myocarditis case series of 9 Turkish patients, we studied: 1) the concentration-to-dose (C/D) ratio; 2) minimum therapeutic dose required to reach 350 ng/ml (a marker for PM status); and 3) titration speed. **Results:** All 4 patients were possible clozapine PMs (their respective minimum therapeutic doses were: 134, 84, 119 and 107 mg/day). The identified possible contributors to clozapine PM status were: 1) valproate in Cases 1, 2 and 4; 2) obesity and a urinary tract infection in Case 2; and 3) obesity and very rapid titration in Case 4. Case 3, who was given a normal US titration, appeared to be a genetic clozapine PM. He developed clozapine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome after rechallenge using 12.5 mg/day > 3 months later. The results were similar to 9 Turkish cases, all of which were PMs (6 on valproate, 4 with obesity, 1 with infection and 1 possibly genetic). **Conclusions:** Future studies using clozapine levels and considering the role of clozapine PM status should explore whether or not all cases of clozapine-induced myocarditis could be explained by lack of individualized titration.

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INTRODUCTION

In 1980, Vesterby et al. published in Danish the first case of clozapine-induced myocarditis in a patient started on 300 mg/day with no up-titration. The typical postmortem presentation is eosinophilic myocarditis (Meeker et al., 1993; Chopra & de Leon, 2016), indicating that clozapine-induced myocarditis may be a hypersensitivity drug reaction associated with rapid titration (de Leon et al., 2016; De las Cuevas et al., 2021). This hypersensitivity reaction may be similar to lamotrigine's Stevens-Johnson syndrome, which led the manufacturer to slow the recommended lamotrigine titration in average patients with further slowing by half for those on valproate, an inhibitor of lamotrigine metabolism (Wang et al., 2015). Therefore, using slow personalized titration may also prevent myocarditis in clozapine patients (de Leon et al., 2022).

The United States (US) package insert recommends starting with a 25-mg dose and targets of 100 mg/day on day 7, 200 mg/day on day 14 and 300 mg/day on day 21; it does not mention clozapine poor metabolizers (PMs) (de Leon et al., 2020a). CYP1A2 is the major metabolic pathway for clozapine leading to norclozapine. Male smokers have the highest CYP1A2 activity and female non-smokers the lowest.

Clozapine metabolism is reflected by the trough steady-state clozapine concentration-to-dose (C/D) ratio, obtained by dividing the serum clozapine concentration (ng/ml) by the clozapine daily dosage (mg/day). A very low C/D ratio indicates an individual with very fast metabolism, while a very high C/D ratio indicates one with very slow metabolism. The clozapine therapeutic range is 350-600 ng/ml (Hiemke et al., 2018). Thus, dividing 350 by the clozapine C/D ratio provides the minimum therapeutic dosage of clozapine of an individual patient or the mean of a group of patients. In 6 samples of European Caucasians (Schoretsanitis et al., 2021), the minimum therapeutic concentration ranged from around 250 mg/day (350 ng/ml/1.48 ng/ml per mg/day=236 mg/day) in female non-smokers to around 400 mg/day (350 ng/ml/0.95 ng/ml per mg/day=368 mg/day) in male smokers. In the US for not-well-understood reasons, minimum therapeutic dosages are considered to range from 300 mg/day in female non-smokers to 600 mg/day in male smokers, corresponding to clozapine C/D ratios of 1.17 to 0.58 ng/ml per mg/day (de Leon et al., 2022).

Clozapine genetic PMs may be explained by CYP1A2 mutations (Ruan & de Leon, 2020). Allorge et al. (2003) described the first clozapine PM, a French non-smoking female who needed a minimum therapeutic dosage of 81 mg/day (Ruan & de Leon, 2020). She had a heterologous state of the CYP1A2*7 allele. This allele has never been described in any other clozapine PM (Ruan et al., 2019a) and is very rare since it is present in <0.1% of European Caucasians (Zhou et al., 2017). The CYP1A2*6 allele has no CYP1A2 activity but has never been studied in clozapine patients. It is present in 0.9% of European Caucasians (Zhou et al., 2017).

Clozapine PMs due to phenoconversion may be more frequent than genetic PMs (Ruan & de Leon, 2020). Phenoconversion can be explained by co-prescription of potent inhibitors of clozapine metabolism, such as fluvoxamine, or moderate inhibitors, such as oral contraceptives (Schoretsanitis et al., 2020). Valproate can be an inhibitor or an inducer of clozapine metabolism, which varies over time and with the individual. As the inductive effects (probably more evident with norclozapine) take several weeks to take effect, inhibition of the parent compound, clozapine, may be more relevant during titration (de Leon, 2020). Valproate pharmacokinetic effects, inhibition or induction, are mediated by the free valproate in serum. Aspirin increases total valproate concentration by inhibiting its metabolism through β-oxidation and further increases free valproate concentration by displacing it from serum proteins (Riesselman et al., 2013). Obesity can reduce CYP1A2 activity (Zarezadeh et al., 2021), increasing clozapine serum concentration (Diaz et al., 2018) and potentially resulting in clozapine PM status (Ruan et al, 2019b). Systemic inflammation with elevations in c-reactive protein (CRP) can lead to clozapine PM status by releasing cytokines which inhibit CYP1A2 (White, 2021). A titration that is too fast for a specific patient can lead to clozapine-induced inflammation with cytokine release (Ruan et al., 2020), increasing clozapine serum concentration and creating positive feedback for clozapine-induced inflammation (de Leon et al, 2020a).

Published reviews of clozapine-induced myocarditis have not paid attention to the possible role of antipsychotic co-medication; thus we were surprised that in our analyses of 3000 myocarditis patients, olanzapine and quetiapine increased the risk of seriousness of clozapine-induced myocarditis in a logistic regression model (De las Cuevas et al.,

2021). In these models, the strength of the association (called effect size by statisticians) is measured by the odds ratio (OR) and its 95% confidence intervals (CIs). As they can decrease clozapine metabolism, expected significant ORs were 1.67 (CI 1.28 to 2.37) for valproate and 2.35 (CI 1.58 to 3.49) for infection. The unexpected significant ORs were 2.83 (CI 1.82 to 4.40) for quetiapine and 1.90 (CI 1.25 to 2.68) for olanzapine. For fatal outcomes the quetiapine OR was significant at 2.12 (CI 1.03 to 4.35) but valproate, infection and olanzapine were not. Olanzapine is metabolized by CYP1A2 and in a situation when this enzyme is saturated by clozapine and the inhibition of cytokines, olanzapine can act as a competitive inhibitor of clozapine metabolism. Quetiapine may contribute to an increase in the severity and lethality of clozapine-induced myocarditis by pharmacodynamic mechanisms, since it may carry a low risk of causing myocarditis by itself in overdoses or too-fast titration (Bhogal et al., 2018).

Five cases of clozapine-induced myocarditis in a New York Hospital were reinterpreted as associated with too-rapid titration for each patient (de Leon et al., 2020b). One appeared to behave as a clozapine PM since he/she was unable to tolerate a dose of 25 mg/day. Two other patients had clozapine concentrations providing very low minimum therapeutic doses of 95 and 109 mg/day. Table 1 presents the one prior article that describes 9 cases from a Turkish hospital with their minimum therapeutic doses, risk factors and titrations (Ertuğrul et al., 2021). These 9 cases appear to be compatible with the hypothesis that clozapine-induced myocarditis and other clozapine-induced inflammations may be associated with titration that is too fast for that specific patient. One Turkish patient appeared to be a genetic PM since he had no risk factor such as valproate, obesity or infection.

Using as our methodology that of the Turkish case series (Ertuğrul et al., 2021), we explored the hypothesis that the 4 US patients with clozapine-induced myocarditis were clozapine PMs. The minimum therapeutic doses leading to 350 ng/ml were estimated using clozapine C/D ratios and their titrations were carefully reviewed.

METHODS

Eastern State Hospital is a US psychiatric hospital located in Lexington, KY. The first clozapine-induced myocarditis case occurred in 2005 but was not published until 2016 (Chopra & de Leon, 2016). This article includes three later cases diagnosed in 2016 (Case 1), 2018 (Case 2) and 2019 (Case 3). Our institutional review board does not require written consent for publication of retrospective case reports following standard clinical care, but nevertheless Case 1 provided verbal consent for publication and Cases 2 and 3 written consent. Early morning collections are used as trough serum clozapine concentrations. In normal circumstances we wait at least 5 days after any clozapine dose changes to draw blood. This is based on half-life of 1 day and 5 half-lives for steady-state concentrations. In urgent situations not allowing for a 5-day wait, we approximate clozapine C/D ratios by using the average dose over the last 5 days (de Leon et al., 2020b; Ruan et al., 2020). Case 4 was diagnosed in Atlanta, Georgia. It was originally published in 2015 (Cook et al., 2015) but the publication did not calculate the clozapine C/D ratio or interpret it as being compatible with clozapine PM status. In each patient, the rapidness of titration during the first and second week was compared to the minimum therapeutic dosage for that patient using a classification (Ertuğrul et al., 2021) based on maximum recommended increases in a textbook (Taylor et al., 2018). In each patient, the highest prescribed clozapine dose was determined whether or not to be considered an overdose by comparing it to the minimum therapeutic dosage for that patient using a classification previously developed (Ertuğrul et al., 2021).

RESULTS

US Case 1

US Case 1 was 46-year-old Caucasian male who was admitted due to schizophrenia. At the hospital, he did not smoke but took omeprazole, a weak CYP1A2 inducer with effects equivalent to smoking (see footnote a of Table 2). His BMI was 24.0 Kg/m^2. He was taking 1500 mg/day of valproate and 81 mg/day of aspirin. The titration did not consider the possibility of clozapine PM status. On day 8 he developed chest pain, the first symptom of myocarditis. On day 15, the CRP was elevated. On day 22 he was taken to the emergency department of a medical hospital. On day 25, an echocardiogram confirmed the diagnosis of myocarditis and clozapine was discontinued. The approximated minimum therapeutic dose was 134 mg/day, which is much lower than the maximum therapeutic 600 mg/day expected for a US male smoker.

US Case 2

US Case 2 was a 34-year-old nonsmoking Caucasian female diagnosed with schizoaffective disorder (see footnote a of Table 3). Her BMI was 34.0 Kg/m^2. Valproic acid was initiated. On day 16 she had sinus tachycardia and the clozapine dosage was decreased. On day 19 clozapine was stopped since she had definitive signs of myocarditis with fever, CRP and troponin elevations. She was transferred to the emergency department of the medical hospital where she was also diagnosed with a urinary tract infection. On day 20 an echocardiogram confirmed the diagnosis of myocarditis. The approximated minimum therapeutic dose was 84 mg/day, which is much lower than the maximum therapeutic 300 mg/day expected for a US female non-smoker.

US Case 3

US Case 3 was a 27-year-old Caucasian non-smoking male with a diagnosis of schizoaffective disorder (see footnote a of Table 4). His BMI was 22.7 Kg/m^2. On day 7, an improvement in psychosis was obvious but on day 11 he developed eosinophilia. He was treated with a relatively conservative titration (on day 7: 100 mg/day and on day 14: 150 mg/day). On day 15 (with a dose of 200 mg/day), he developed chest pain, tachycardia and elevations of CRP and troponin. After a transfer to the emergency department, the cardiologist diagnosed clozapine-induced myocarditis and clozapine was discontinued. The approximated minimum therapeutic dose was 119 mg/day, which is much lower than the maximum therapeutic dosage of 475 mg/day expected for a US male non-smoker. Clozapine rechallenge was elected for this patient because his psychosis failed to respond to other antipsychotics. On day 149, a slow titration was started at 12.5 mg/day but was not further advanced because on day 151 he developed a macopapular rash. On day 162 the 12.5 mg/day of clozapine was stopped after an EKG was compatible with acute pericarditis. The skin rash and eosinophilia on day 162 was compatible with clozapine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (de Filippis et al., 2020).

US Case 4

US Case 4 was a 44-year-old nonsmoking African-American female diagnosed with schizoaffective disorder (see footnote a of Table 5). Her BMI was 31.6 Kg/m^2. A relatively rapid titration was started while taking 1500 mg/day of valproate. On day 16, the diagnosis of myocarditis was considered and was confirmed on day 18. The approximated minimum therapeutic dose was 107 mg/day, which is much lower than the maximum therapeutic dose of 300 mg/day expected for a US female non-smoker. As the original article described (Cook et al., 2015), the titration was too rapid.

DISCUSSION

All 4 patients were possibly clozapine PMs (their respective minimum therapeutic doses were: 134 mg/day (US Case 1), 84 mg/day (US Case 2), 119 mg/day (US Case 3) and 107 mg/day (US Case 4).

The identified possible contributors to clozapine PM status were: 1) valproate in Cases 1, 2 and 4; 2) obesity and a urinary tract infection in Case 2; and 3) obesity and very rapid titration in Case 4. Case 3, who was treated using a normal US titration, appeared to be a genetic clozapine PM. He developed clozapine-induced DRESS syndrome after rechallenge with 12.5 mg/day more than 3 months later.

Comparison with the Turkish case series and the combination of the two samples

Risk factors and minimum therapeutic doses appear similar to the Turkish cases, so we combined them in Table 1. After combining these 4 US patients with 9 Turkish patients, we found that all 13 patients were PMs. Moreover, 5 of them were classified as extremely PM with very low minimum therapeutic doses ranging from 72 to 134 mg/day, which would be very unexpected for their treating physicians.

The most frequent risk factors were valproate in 9 patients, obesity in 6 and infections in 2. Two patients were on quetiapine or olanzapine. Regarding the rapidness of titration compared with their individual minimum therapeutic dosage, 8 were rapid in the first week and 9 in the second. The final dose was too high for the minimum therapeutic dose of the patient in 11 of 13 patients. Only in one patient was the titration not too rapid for the minimum therapeutic dose: Turkish Case 4, who had no known risk factors and appeared to be a genetic PM. US Case 3, who appeared to be a genetic PM, developed myocarditis after a completely normal titration for an average US patient and DRESS after a clozapine rechallenge with 12.5 mg/day.

Limitations

This is a retrospective analysis of clozapine levels undertaken to estimate minimum therapeutic doses and possible PM status. The system used to identify possible clozapine PMs and assess titrations (Ertuğrul et al., 2021) was developed in 2021 by the last author to retrospectively assess cases collected. Three cases were collected in his US psychiatric hospital while 10 other cases were previously published (Cook et al., 2015; Anıl Yağcıoğlu et al, 2019) by authors who did not know that many years later the last author would ask to reanalyze them. Table 1 indicates that in 12/13 cases the clozapine minimum therapeutic dose was approximated since steady-state levels could not be measured in the middle of an urgent situation and these approximations reflect a moment in time when inflammation was present and interfering with clozapine metabolism. Once clozapine is discontinued during clozapine-induced myocarditis it is not possible to establish clozapine therapeutic minimum doses unless a successful rechallenge occurs (Danilewitz et al., 2021).

CONCLUSION

Future prospective studies of clozapine-induced myocarditis with repeated measures of clozapine C/D ratios and estimations of minimum therapeutic dosing need to further examine whether clozapine PM status may be a risk factor for clozapine-induced myocarditis. Valproate, obesity and infections appear to be risk factors in both samples but future studies need to further establish them as likely contributing factors for clozapine-induced myocarditis. The contribution of genetic PMs or co-prescription of olanzapine and quetiapine need independent replication. Until these studies are published, we recommend (de Leon et al., 2022): 1) use of extraordinarily slow clozapine titration when there is concern for PM status or risk factors like obesity, valproate co-prescription or infection; 2) when available, consideration of weekly monitoring of clozapine concentrations during titration; and 3) weekly measuring of c-reactive protein and troponin to screen for clozapine-induced myocarditis (Goldsmith & Cotes, 2017).

Table 1. Association of clozapine-induced myocarditis and clozapine PM status

Country Case	Stop Day D[c]	Age-sex-smoking	PM status[a] minimum therapeutic D (for 350 ng/ml)	Risk factors			Rapid titration Week		Overdose[b]	AP
				Inf	Obesity[d]	VPA	First[e]	Second[f]		
Turkish 1 Died	14 125	65 yo ♀ unknown	Yes (Mildly PM) *124* (124/236=0.53)	No	No	Yes	No	Yes (Mildly) (40 to 101%)	Yes (Mildly) 125 (125/12=1.01)	QUE
Turkish 3	20 200	27 yo ♀ non-smoker	Yes (PM) *141* (141/236=0.60)	No	No	Yes	Yes (Mildly) (0 to 53%)	No	Yes (Mildly) 200 (200/141=1.40)	No
Turkish 4 Genetic	20 125	32 yo ♂ smoker	Yes (PM) *141* (141/368=0.38)	No	No	No	No	No	No	No
Turkish 5	16 250	27 yo ♀ non-smoker	Yes (Mildly PM) *260* (260/368=0.71)	No	No	Yes	No	Yes (Mildly) (29 to 96%)	No	No
Turkish 6	18 400	23 yo ♂ non-smoker	Yes (Mildly PM) *154* (154/256=0.60)	No	Yes	No	Yes (Rapid) (0 to 97%)	Yes (Mildly) (97 to 195%)	Yes (Very) 400 (400/145=2.60)	Other
Turkish 7	22 300	48 yo ♀ smoker	Yes (Extremely PM) 83 (83/357=0.23)	No	Yes	No	Yes (Very) (0 to 120%)	Yes (Very) (120 to 301%)	Yes (Extremely) 300 (300/83=3.61)	OLA
Turkish 8	20 200	19 yo ♀ non-smoker	Yes (PM) *130* (130/236=0.55)	Yes	Yes	Yes	No	Yes (Rapid) (38 to 154%)	Yes (High) 200 (200/130=1.54)	OLA
Turkish 9	19 150	52 yo ♂ non-smoker	Yes (PM) *116* (116/256=0.45)	No	No	Yes	Yes (Mildly) (0 to 65%)	Yes (Mildly) (65 to 129%)	Yes (Mildly) 150 (150/116=1.29)	Other
Turkish 10	16 150	23 yo ♂ non-smoker	Yes (Extremely PM) *72* (72/256=0.28)	No	Yes	Yes	Yes (Mildly) (0 to 139%)	Yes (Mildly) (139 to 208%)	Yes (Very) 150 (150/72=2.08)	Other
US 1	25 250	46 yo ♂ omeprazole	Yes (Extremely PM) *134* (134/600=0.21)	No	No	Yes	No 0 to 37%	Yes (Mildly) (37% to 112%)	Yes (Very) 250 (250/134=2.08)	Other
US 2	18 150	34 yo ♀ non-smoker	Yes (Extremely PM) *84* (134/300=0.28)	Yes	Yes	Yes	Yes (Mildly) (0 to 69%)	Yes (Mildly) (69 to 119%)	Yes (High) 150 (150/84=1.79)	Other
US 3 Genetic	16 200	27 yo ♂ non-smoker	Yes (Extremely PM) *119* (119/475=0.25)	No	No	No	Yes (Rapid) 0 to 84%	No (84% to 126%)	Yes (High) 200 (200/119=1.68)	QUE
US 4	16 500	44 yo ♀ non-smoker	Yes (Extremely PM) *107* (107/300=0.36)	No	Yes	Yes	Yes (Very) (0 to 374%)	No (374 to 420%)	Yes (Extremely) 500 (500/107=4.67)	Other
Total	14-25 125-500	7 ♀ & 6 ♂	13 Yes *72-260*	2 Yes	6 Yes	9 Yes	8 Yes	9 Yes	11 Yes	2 QUE 2 OLA
				2 possible genetic						

AP: antipsychotic; D: dose; inf: infection; OLA: olanzapine; PM: poor metabolizer; QUE: quetiapine; Other: other than OLA or QUE; US: United States.

Minimum therapeutic Ds shown in italics are rough approximations due to lack of steady-state.

[a] PM status was classified according to severity. The mean dosage for European Caucasians based on their sex and smoking status was used as a control for comparison with the Turkish cases and the mean dosage of US patients was used for US cases. The severity of the PM status was classified as: 1) mildly PM: who needed half to ¾ of the minimum therapeutic D of an average control with the same sex and smoking status; 2) PM: only needed half, but >1/4, of the minimum therapeutic D for an average control with the same sex and smoking status; and 3) extremely PM: only needed <¼ of the minimum therapeutic D of the stratified group for an average control with the same sex and smoking status.

[b] The ratio between the maximum prescribed D and the minimum therapeutic dose estimated for that patient was calculated. This ratio was used to classify the final D as an overdose. The overdose was classified as: a) mildly high: a final D which was 1.01-1.51-fold higher than the minimum therapeutic D for that specific patient, 2) high: a D 1.51-2.00 times higher than the minimum therapeutic D for that specific patient, 3) very high: a D between 2.01-3.00 times higher than the minimum therapeutic D, and 4) extremely high: a D >3.00 times higher than the minimum therapeutic D (Ertuğrul et al., 2021).

[c] D refers to maximum prescribed D during the titration before stopping the clozapine.

[d] A longitudinal study in a randomized clinical trial (Diaz et al., 2018) suggested that a weight increase is linearly associated with a decrease in clozapine metabolism. Based on Asian samples, some patients with BMI>29 Kg/m2 appear to behave as clozapine PMs (Ruan et al., 2019b); thus, a BMI>29 Kg/m2 was defined as obesity with risk of being associated with a clozapine PM phenotype (Ertuğrul et al., 2021).

[e] In the textbook by Taylor et al. (2018) the maximum recommended increase during the first week of targeted Ds was in female non-smokers. The maximum recommended titration increase in the first week was from 0 to 40% of the targeted D. An increase from 0 to >40% of the minimum therapeutic D for that patient was considered rapid. Within rapid titration the classifications were: 1) mildly rapid: from 0% to between 41-80% of the minimum therapeutic D for that specific patient, 2) rapid: a titration from 0% to between 81-120%, 3) very rapid: a titration from 120% to >180%, and 4) extremely rapid >180% (Ertuğrul et al., 2021).

[f] In the textbook by Taylor et al. (2018) the maximum recommended increase during the second week of the targeted D was in female non-smokers. The maximum recommended titration was to increase the D by 60% in the second week, from 50% to 110% of the targeted D. An increase by >60% of the minimum therapeutic D for that patient was considered rapid. Within the rapid titrations they were classified as: 1) mildly rapid: an increase by between 61-120%, 2) rapid: between 120-180% , 3) very rapid: between 181-240%, and 4) extremely rapid: >240% (Ertuğrul et al., 2021).

Table 2. Clozapine-induced myocarditis: Case 1[a]

Day[b]	CLO			C/D ratio		VPA		Laboratory Markers				Heart		
	D mg/day	C/NCLO ng/ml	Total ng/ml	ng/ml per mg/day CLO	Total	D/Asp[c] mg/day	C mcg/ml	CRP (0-0.9) mg/dL	Trop T (<0.010 ng/ml	ESR (0-11) mm/hr	Eos (0-0.5) k/μL	EKG	Echo	Symptoms/signs
1[d]	5					1500/81		0.10	<0.010		0.75	N		
4[e]	50					1500/81								
7[e]	50					1500/81								"felt better and more stable"
8[f]	100					1500/81	81		<0.010		1.06	N		Chest pain in the morning[g]
13[h]	150					1500/81								
15[i]	150					1500/81		10.0	<0.010					Hypotension and tachycardia[j]
16[k]	200					1500/81								
19[l]	250					1500/81								
22[m]	0	603/140	743[n]	2.62[n]	3.23[n]	500/81		18.5	<0.010	105	0.61	Abn[o]		Hypotension[p]
23[q]	250					1500						Abn[o]		
24[q]	200					1500					0.37			
25[q]	100					1500							Abn[r]	
26[s]	0					1500								Symptoms improved rapidly[s]

Asp: aspirin; C: concentration; C/D: concentration-to-dose; CLO: clozapine; CRP: C-reactive protein; D: dose; Echo: echocardiogram; EKG: electrocardiogram; Eos: Absolute eosinophil count; ESR: erythrocyte sedimentation rate; NCLO: norclozapine; PM: poor metabolizer; Total: CLO + NCLO C; Trop T: Troponin T; US: United States.
Definitive abnormalities possibly explained by clozapine-induced myocarditis are described in red font.

[a] The patient was a 46-year-old Caucasian male who was admitted due to schizophrenia. This was his 19th admission to this facility and the 3rd admission in the previous month. Before coming to the non-smoking hospital, he smoked 1 pack/day of cigarettes. At admission he refused a nicotine patch to prevent nicotine withdrawal. His BMI was 20.4 Kg/m^2. For gastroesophageal reflux disease he was treated with omeprazole which is a mild inducer of CYP1A2 with activity similar to smoking. Other medical problems were hypertension treated with metoprolol, dyslipidemia treated with atorvastatin, hypothyroidism treated with levothyroxine, and chronic constipation treated with docusate. He also took aspirin daily. These medications were continued during this hospitalization in addition to adding ferrous sulfate for iron deficiency anemia discovered on initial laboratory evaluation.

[b] Day # is in relation to initiation of clozapine and not total hospital stay. In the first week, the patient had the CLO D increased from 0 to 37% of his minimum therapeutic D (50/134=0.37). In the second week the D increased by 75%, from 37% to 112% (150/134=1.12), indicating a mildly rapid titration.

[c] The patient was prescribed 81 mg/day of aspirin for cardiovascular protection. Valproate pharmacokinetic effects including inhibition are mediated by the free valproate in serum. Aspirin increases total valproate concentration by inhibiting its metabolism through β-oxidation and further increases free valproate concentration by displacing it from serum proteins (Riesselman et al., 2013).

[d] Haloperidol 10 mg/day, atorvastatin 10 mg/day, benztropine 2 mg/day, docusate 100 mg/day, ferrous sulfate 325 mg/day, levothyroxine 75 μg/day, metoprolol 25 mg/day, omeprazole 20 mg/day, hydroxyzine 50 mg/day and intramuscular injections (chlorpromazine 100 mg/day, diphenhydramine 50 mg/day, lorazepam 4 mg/day, and haloperidol 5 mg/day).

[e] Haloperidol 10 mg/day, atorvastatin 10 mg/day, benztropine 2 mg/day, docusate 100 mg/day, ferrous sulfate 325 mg/day, levothyroxine 75 μg/day, metoprolol 25 mg/day, omeprazole 20 mg/day.

[f] Haloperidol 10 mg/day, atorvastatin 10 mg/day, benztropine 2 mg/day, docusate 100 mg/day, ferrous sulfate 325 mg/day, levothyroxine 75 μg/day, metoprolol 25 mg/day, omeprazole 20 mg/day and hydroxyzine 50 mg/day.

[g] Reported non-radiating central chest pain in the morning. Resolved spontaneously by the afternoon.

[h] Haloperidol 10 mg/day, benztropine 2 mg/day, docusate 100 mg/day, ferrous sulfate 325 mg/day, levothyroxine 75 μg/day, metoprolol 25 mg/day and omeprazole 20 mg/day.

[i] Haloperidol 10 mg/day, benztropine 2 mg/day, docusate 100 mg/day, ferrous sulfate 325 mg/day, levothyroxine 75 μg/day, metoprolol 25 mg/day, omeprazole 20 mg/day, hydroxyzine 50 mg/day and melatonin 10 mg/day.

[j] The patient reported that he "felt dizzy". Vital signs notable for hypotension (91/62 mmHg) and tachycardia (112 beats/minute). He reported that he felt better after drinking fluids. He denied chest pain, chest pressure, and heart palpitations.

[k] Haloperidol 10 mg/day, benztropine 2 mg/day, docusate 100 mg/day, ferrous sulfate 325 mg/day, levothyroxine 75 μg/day, metoprolol 25 mg/day, omeprazole 20 mg/day, hydroxyzine 50 mg/day and acetaminophen 650 mg/day.

[l] Benztropine 1 mg/day, docusate 100 mg/day, ferrous sulfate 325 mg/day, levothyroxine 75 μg/day, metoprolol 25 mg/day, omeprazole 20 mg/day, acetaminophen 650 mg/day

[m] Docusate 100 mg/day, ferrous sulfate 325 mg/day, levothyroxine 75 μg/day, omeprazole 20 mg/day, acetaminophen 650 mg/day. Metoprolol was discontinued because of persistent hypotension.

[n] A commercial laboratory using liquid chromatography-mass spectroscopy-mass spectroscopy measured serum clozapine and norclozapine concentrations. This was a trough C but it was not steady state since the patient was on 250 mg/day only for 3 days. As C was not in steady state, we approximated the dosing by calculating the mean D from the last 5 days (200-200-250-250-250), which was 230 mg/day. This D was used to calculate the clozapine C/D ratio (603/230=2.62) and total CD ratio (743/230=3.23). The approximated clozapine C/D ratio of 2.62 ng/ml per mg/day provides a minimum therapeutic D of 134 mg/day. This is much lower by a factor of 0.21 (136/600=0.21) than the typical minimum therapeutic D of US male smokers of 600 mg/day. This is compatible with a CLO PM (in our system of classification, an extremely PM). It is likely that inflammation which was associated with rapid titration, by releasing cytokines, further contributed to the inhibitory effects associated with valproate on CLO metabolism.

[o] Normal sinus rhythm; ST elevation, consider early repolarization versus cardiac injury.

[p] The patient reported dizziness, vague left arm pain, and generalized weakness. Vital signs were notable for hypotension (88/60 mmHg). He was taken to the emergency room.

[q] Docusate 200 mg/day, ferrous sulfate 325 mg/day, levothyroxine 75 μg/day, pantoprazole 40 mg/day, nicotine patch 14 mg/24hr, subcutaneous enoxaparin 40 mg/day.

[r] Ejection fraction of 50-55%. Borderline reduced left ventricular function and global hypokinesis.

[s] Clozapine was discontinued, and the patient's hypotension, dizziness, and fatigue improved shortly thereafter. The cardiologist did not recommend additional evaluation or treatment. The psychiatrist switched the patient to haloperidol. The patient improved from the medical and psychiatric standpoints and was discharged on day 34.

Table 3. Clozapine-induced myocarditis: Case 2[a]

Day[b]	CLO			C/D ratio		VPA		Laboratory Markers			Heart		
	D	C/NCLO	Total	ng/ml per mg/day		D	C	CRP (0-0.9)	Trop T (<14)	Eos (0-0.5)	EKG	Echo	
	mg/day	ng/ml	ng/ml	CLO	Total	mg/day	mcg/ml	mg/dL	ng/L	k/μL			Symptoms/signs
0[c]								0.2	<6	0.14	AV block[d]		
1[e]	25					500							
2[e]	25					1000							
6[f]	50					1000		<0.1	<6	0.16			
9[g]	75					1000							
13[h]	100					1000	66	0.2	<6	0.16			
16[i]	150					1000					Sinus tachycardia		
18[j]	75					1000							
19[k]	0	477/105[l]	582[l]	4.15[l]	5.06[l]	1000	56	16.9	30[m]	0.30	Sinus tachycardia[n]		Fever, hypotension, fatigue[o]
20[k]	0					1000						Abn[p]	At general hospital[q]
21[k]	0					1000							At general hospital[q]
22[r]	0					1000							Back to psychiatric hospital[s]
23[t]	0					1000					AV block[d]		

C: concentration; CBC: complete blood count; C/D: concentration-to-dose; CLO: clozapine; CRP: C-reactive protein; D: dose; Echo: echocardiogram; EKG: electrocardiogram; Eos: Absolute eosinophil count; NCLO: norclozapine; PM: poor metabolizer; Total: CLO + NCLO C; Trop T: high sensitivity Troponin T; US: United States.
Definitive abnormalities possibly explained by clozapine-induced myocarditis are described in red font.

[a] A 34-year-old Caucasian female nonsmoker was transferred from a local prison to the psychiatric hospital. Her BMI was 34.0 Kg/m^2. She was first diagnosed with schizoaffective disorder 15 years ago, but her symptoms had not responded to several trials of antipsychotic polytherapy. She was taking ziprasidone, bupropion, and fluoxetine at the time of admission. On initial examination, the patient endorsed auditory hallucinations as well as tangential and intermittently disorganized thoughts. Bupropion and fluoxetine were discontinued shortly after admission. Valproic acid was initiated as both a mood stabilizer and for seizure prophylaxis since she had a history of seizure disorder.

[b] Day # is in relation to initiation of clozapine and not total hospital stay. In the first week, the patient had the CLO D increased from 0 to 69% of her minimum therapeutic D (50/84=0.69), indicating a mildly rapid titration. In the second week the D increased by 50% from 69% to 119% (100/84=1.19), indicating a mildly rapid titration.

[c] Ziprasidone 160 mg/day.

[d] Sinus rhythm with first degree atrioventricular block; otherwise normal EKG.

[e] Ziprasidone 120 mg/day and olanzapine 5 mg/day.

[f] Ziprasidone 100 mg/day, olanzapine 5 mg/day and melatonin 10 mg/day.

[g] Ziprasidone 80 mg/day, olanzapine 5 mg/day and melatonin 10 mg/day.

[h] Ziprasidone 80 mg/day, olanzapine 10 mg/day, melatonin 10 mg/day, omeprazole 40 mg/day, and ibuprofen 400 mg/day for pain.

[i] Ziprasidone 60 mg/day, melatonin 10 mg/day, omeprazole 40 mg/day, and ondansetron 8 mg/day for nausea.

[j] Ziprasidone 40 mg/day, melatonin 10 mg/day, and omeprazole 40 mg/day.

[k] Ziprasidone 40 mg/day, melatonin 10 mg/day, omeprazole 40 mg/day, intravenous ceftriaxone 1000 mg/day for urinary tract infection, and subcutaneous enoxaparin 40 mg/day.

[l] A commercial laboratory using liquid chromatography-mass spectroscopy-mass spectroscopy measured serum clozapine and norclozapine concentrations. This was a trough C but it was not steady state since the patient was on 150 mg/day only for 3 days. As the concentration was not in steady state, we approximated the dosing by calculating the mean D from the last 5 days (100-100-150-150-75), which was 115 mg/day. This D was used to calculate the clozapine C/D ratio (477/115=4.15) and total CD ratio (582/115=5.06). The approximated clozapine C/D ratio of 4.15 ng/ml per mg/day, which provides a minimum therapeutic D of 84 mg/day (350/4.15=84), is much lower by a factor of 0.21 (84/300=0.28) of the typical minimum therapeutic D of US female non-smokers of 300 mg/day. This is compatible with being a CLO PM (in our system of classification, an extremely PM). It is likely that the inflammation, which was associated with the rapid titration by releasing cytokines, further contributed to the inhibitory effects associated with the effects of a urinary tract infection, valproate and obesity on CLO metabolism.

[m] At the state hospital Trop T was 30 ng/L (<14 ng/L). These findings were suggestive of clozapine-induced myocarditis. Clozapine was therefore discontinued and the patient was promptly transferred to the emergency department. She was subsequently admitted to a general medicine service for further evaluation and management. Trop T, collected q 2 hours decreased from the initial value of 30 to 23 and then 18 ng/L.

[n] Sinus tachycardia with non-specific T-wave changes in inferior, inferolateral, and high lateral leads when compared to the EKG on Day 16.

[o] The patient reported fatigue, chest pain, abdominal pain, nausea, diarrhea, and body aches, in addition to feeling "feverish" for the past couple of days. Vitals in emergency department: hypotensive (94/58 mmHg), tachycardic (130 beats/minute), and febrile (38.7°C).

[p] Ejection fraction of 60-80%, no wall motion abnormalities, and trace pericardial effusion.

[q] Plasma fibrin D-dimer was elevated, but computerized tomography protocol ruled out pulmonary thromboembolism and other pulmonary pathology. Computerized tomography of the abdomen and pelvis, ordered to evaluate abdominal pain, did not identify any inflammatory process or evidence of bowel obstruction. Urinalysis revealed findings consistent with a urinary tract infection. Chest x-ray, CBC, comprehensive metabolic panel, lipase, lactic acid and blood cultures were unremarkable. Given the patient's age, lack of coronary artery disease risk factors, and results of laboratory and radiologic studies, a diagnosis of clozapine-induced myocarditis was made by the cardiologist. The patient was treated with intravenous fluids and acetaminophen, which improved blood pressure, heart rate, and temperature. In addition, the patient was treated with a 3-day course of ceftriaxone for the urinary tract infection.

[r] Ziprasidone 40 mg/day, melatonin 10 mg/day, omeprazole 40 mg/day, and subcutaneous enoxaparin 40 mg/day.

[s] Chest pain, as well as other symptoms mentioned on Day 19, improved and she was sent back to the psychiatric hospital.

[t] Ziprasidone 40 mg/day, melatonin 10 mg/day, omeprazole 40 mg/day, and risperidone 1 mg/day.

Table 4. Clozapine-induced myocarditis: Case 3[a]

Day[b]	CLO			C/D ratio		Laboratory Markers					Heart		
	D	C/NCLO	Total	ng/ml per mg/day		CRP (0-0.9)	hsCRP (<10)	Trop T (<0.010)	ESR (0-11)	Eos (0-0.5)	EKG	Echo	
	mg/day	ng/ml	ng/ml	CLO	Total	mg/dL	mg/L	ng/mL	mm/hr	k/μL			Symptoms/signs
1[c]	25							<0.010		0.49	Normal		
5[d]	50												
7[d]	100												Improvement of psychosis[e]
11[d]	125					0.2		<0.010		0.66			
12[d]	150												
14[d]	150												
15[d]	200					4.9		0.081		0.65	Tachycardia[f]		General hospital: Chest pain[g]
16[h]	50	454/215[i]	669[i]	2.93[i]	4.32[i]	9.1		0.067[j]		0.66		Normal[k]	General hospital: Fatigue[l]
17[m]	0												Back to psychiatric hospital
21[n]	0					6.6		<0.010		0.65	Normal		
23[o]	0					2.0							
49[p]	0					0.2				0.41	Normal		
>50						Clozapine cannot be restarted[q]							
148[r]	0					0.1		<0.010	5	0.48			
149[s]	12.5										Normal		
151[s]	12.5												Macopapular rash[t]
154[u]	12.5										Abormal[v]		Headache[w]
155[u]	12.5					3.1		<0.010	9	0.22			
157[y]	12.5										Abnormal[v]		
158[z]	12.5					2.9	39.2	<0.010	13	0.22			
161[u]	12.5					1.0	10.3	<0.010	7	0.22			
162[u]	0										Acute pericarditis[aa]		Hypotensive[ab]
164[u]	0												Chest pain[ac]
165[ad]	0					0.3	2.8	<0.010		0.58			Felt fine and no chest pain

C: concentration; CBC: complete blood count; C/D: concentration-to-dose; CLO: clozapine; CRP: C-reactive protein; D: dose; Echo: echocardiogram; EKG: electrocardiogram; Eos: Absolute eosinophil count; ESR: erythrocyte sedimentation rate; hs: high sensitivity; NCLO: norclozapine; PM: poor metabolizer; Total: CLO + NCLO C; Trop T: Troponin T; US: United States.
Definitive abnormalities possibly explained by clozapine-induced myocarditis are described in red font.

[a] The patient was a 27-year-old Caucasian male non-smoker with a diagnosis of schizoaffective disorder. His BMI was 22.7 Kg/m^2. This is his 9th hospitalization at this facility. The patient was reportedly stable on quetiapine and sertraline in the past and has decompensated since discontinuing medications while in prison. Upon admission, the patient was restarted on quetiapine and sertraline. Early on in admission, the patient complained of auditory and visual hallucinations, delusions, and paranoia. His appearance was disheveled and he demonstrated hypersexual and aggressive behavior frequently requiring the use of intramuscular injections of chlorpromazine and diphenhydramine. Ziprasidone and lithium were added with minimal improvement in symptoms. The patient has had previous trials of numerous antipsychotic medications including risperidone, olanzapine, and lurasidone. The patient was deemed refractory to treatment and a good candidate for clozapine initiation.

[b] Day # is in relation to initiation of clozapine and not total hospital stay. In the first week, the patient had the CLO D increased from 0 to 84% of his minimum therapeutic D (100/119=0.84), indicating a rapid titration. In the second week the D increased by 42% from 84% to 126% (150/119=1.26).

[c] Quetiapine 800 mg/day, ziprasidone 80 mg/day, lithium 900 mg/day, benztropine 1 mg/day, chlorpromazine 100 mg/day, diphenhydramine 100 mg/day.

[d] Quetiapine 800 mg/day, ziprasidone 80 mg/day, lithium 900 mg/day, benztropine 1 mg/day.

[e] He was calmer and more cooperative, his thoughts were becoming less disorganized, hallucinations improved, and he was meeting his hygiene goals.

[f] Sinus tachycardia; nonspecific T-wave abnormalities.

[g] The patient reported that he "did not feel good." He skipped lunch and stayed in bed. He complained of left-side chest pain, nausea, lightheadedness, and fatigue. He was transferred to the emergency department and subsequently admitted to a general medicine service for further evaluation. CRP increased to 9.1 mg/dL. CBC was notable for a leukocytosis of 12 k/μL with eosinophilia of 0.66 k/μL. Plasma fibrin D-dimer was negative, ruling out pulmonary thromboembolism. With the downward trend in troponins and no other risk factors for coronary artery disease, the consulting cardiologist determined that acute coronary syndrome was unlikely. Given the EKG changes, elevated CRP, eosinophilia, and the recent initiation of clozapine, a diagnosis of clozapine-induced myocarditis was made by the cardiologist and clozapine was discontinued. Given the grossly normal left ventricular function on echocardiogram and no signs of heart failure upon physical examination, no further medical management was recommended. The chest pain and lightheadedness improved by the next day, and he was deemed medically appropriate to be discharged and transferred back to the psychiatric hospital.

[h] Quetiapine 800 mg/day, lithium 900 mg/day and benztropine 1 mg/day.

[i] A commercial laboratory using liquid chromatography-mass spectroscopy-mass spectroscopy measured serum clozapine and norclozapine concentrations. This is a trough C but it was not steady state since the patient was on 200 mg/day only for 1 day. As the concentration was not in steady state, we approximated the dosing by calculating the mean D from the last 5 days (125-150-150-150-200), which was 155 mg/day. This D was used to calculate the clozapine C/D ratio (454/155=2.93) and total C/D ratio (669/155=4.32). The approximated clozapine C/D ratio of 2.93 ng/ml per mg/day provides a minimum therapeutic D of 119 mg/day (350/2.93=119), which is much lower by a factor of 0.25 (119/475=0.25), than the typical minimum therapeutic D of US male non-smokers of 475 mg/day. This is compatible with a CLO PM (in our system of classification, an extremely PM). It is likely that the inflammation, by releasing cytokines, further contributed to decreased CLO metabolism in a possibly genetic PM.

[j] Trop T trended down from 0.067 to 0.062 to 0.059 over the course of the day.

[k] Ejection fraction 52%, normal left ventricular wall motion, and no pericardial effusion.

[l] Difficult to arouse, skipped meals again, difficult to obtain radial pulse. Continued to complain of left-side chest pain, fatigue, and lightheadedness.

[m] Quetiapine 400 mg/day, lithium 450 mg/day, benztropine 1 mg/day, risperidone 1 mg/day, diphenhydramine 100 mg/day, intramuscular paliperidone 234 mg/day.

[n] Lithium 900 mg/day, benztropine 1 mg/day and risperidone 2 mg/day.

[o] Lithium 900 mg/day, benztropine 1 mg/day, risperidone 4 mg/day and lorazepam 4.5 mg/day.

[p] Lithium 900 mg/day, benztropine 1 mg/day, risperidone 2 mg/day, lorazepam 1.5 mg/day and naltrexone 100 mg/day.

[q] Unfortunately, the patient began to decompensate from a psychiatric standpoint after the discontinuation of CLO. He had to be managed with forced medication with frequent intramuscular injections and had a skin infection on his leg. These infections caused CRP to become elevated. CRP normalized once the skin infection resolved and intramuscular injections were minimized. Since CLO was the only medication that improved the patient's psychotic symptoms, the decision was made to rechallenge the patient with CLO.

[r] Lithium 900 mg/day, benztropine 1 mg/day, lorazepam 2 mg/day and haloperidol 20 mg/day.

[s] Lithium 900 mg/day, benztropine 1 mg/day, lorazepam 1 mg/day, haloperidol 20 mg/day and ibuprofen 800 mg/day.

[t] Maculopapular rash appeared on the upper extremities and spread to the abdomen over the next few days.

[u] Lithium 900 mg/day, benztropine 1 mg/day, lorazepam 1 mg/day and haloperidol 20 mg/day.

[v] Normal sinus rhythm; diffuse ST elevation, consider early repolarization, pericarditis, or cardiac injury.

[w] The patient complained of headache, was more withdrawn, and pale. He reportedly had a syncopal episode.

[y] Lithium 900 mg/day, benztropine 1 mg/day, lorazepam 1 mg/day, haloperidol 25 mg/day and diphenhydramine 100 mg/day.

[z] Lithium 900 mg/day, benztropine 1 mg/day, lorazepam 1 mg/day, haloperidol 25 mg/day, diphenhydramine 100 mg/day and ibuprofen 800 mg/day.

[aa] Normal sinus rhythm; diffuse ST elevation, more pronounced than previous EKGs, consistent with acute pericarditis.

[ab] Difficult to arouse from sleep, hypotensive (84/53 mmHg), and bradycardic (44 beats/minute).

[ac] The patient had sharp left-side chest pain. Cardiology recommended ibuprofen and colchicine for pericarditis with outpatient cardiology follow-up in one month.

[ad] Lithium 900 mg/day, benztropine 1 mg/day, lorazepam 1 mg/day, haloperidol 20 mg/day and ibuprofen 1800 mg/day.

Table 5. Clozapine-induced myocarditis: Case 4[a]

Day[b]	CLO			C/D ratio		Valproate		Signs				
	D	C[b]/NCLO	Total	ng/ml per mg/day		D	C	CRP	Troponin T	Pulse	T	
	mg/day	ng/ml	ng/ml	CLO	Total	mg/day	mcg/ml	(0-0.5) mg/dL	(<0.04) ng/ml	beats min	[0]C	Heart/Comments
1[c]	25					1500				82-94	35.7-36.1	
2[c]	50					1500				99-105	35.5-36.1	
3[c]	100					1500				96-97	36.4-36.6	
4[c]	150					1500				96-117	35.1-35.9	
5[c]	200					1500		0.19	<0.01	104-119	35.8-36.3	
6[c]	300					1500				100-112	36.1-36.9	
7[c]	400					1500				96-118	35.1-36.9	
8[d]	500					1500				93-119	35.1-37.0	EKG: sinus tachycardia
9[e]	500					1500				65-104	36.0-36.2	
10[e]	500					1500		0.07	<0.01	80	36.5	Psychosis improved
11[e]	500					1500				80-90	35.5-36.3	Discharge from hospital
12[e]	500					1500						
13[e]	500					1500						
14[e]	500					1500						
15[e]	500					1500						Described as sedated
16	0	1637/574[f]	2211[f]	3.27[g]	4.42[g]	0	104	15.8	0.80	115	37.7	Possible myocarditis
17[h]	0					0		22.6	3.18 & 2.80	106	38.8	Atrial fibrillation
18	0					0			1.27 & 0.91			+ Echocardiogram[i]
19	0					0			0.55 & 0.43			
20	0					0			0.12			
21[j]	0					0			0.09			
22	0					0						
23	0					1500						
24[k]	0					1500			0.02			No signs of myocarditis

[0]C=Celsius degrees; C: concentration; C/D: concentration-to-dose; CLO: clozapine; CRP: C-reactive protein; D: dose; EKG: electrocardiogram; NCLO: norclozapine; PM: poor metabolizer; T: temperature; Total: CLO + NCLO C; US: United States. Definitive abnormalities possibly explained by clozapine-induced myocarditis are described in red font.

[a] The patient was a 44-yo African-American female non-smoker with a baseline BMI of 31.6 Kg/m^2 and diagnosed with schizoaffective disorder and mild intellectual disability.[20]

[b] Day # is in relation to initiation of clozapine and not total hospital stay. In the first week, the patient had the CLO D increased from 0 to 374% of her minimum therapeutic D (400/107=3.74), indicating a very rapid titration. In the second week the D increased by 46% from 374% to 420% (500/119=4.20).

[c] Risperidone 4 mg/day.

[d] Risperidone 2 mg/day.

[e] Risperidone 2 mg/day and metoprolol 50 mg/day.

[f] The concentration was measured by liquid chromatography/mass spectroscopy in a commercial laboratory. It was a steady-state concentration after 8 days of stable dosing. The patient took the last D the night before and did not take a morning D; C was measured at 2 in the afternoon. As more than 12 hours had elapsed since the last D, this C could be considered a trough C.

[g] The CLO C/D ratio was 3.27 (1637/500=3.27) ng/ml per mg/day which provides a minimum therapeutic D of 107 mg/day (350/3.27=107), which is much lower by a factor of 0.36 (107/300=0.36), than the typical minimum therapeutic D of US female non-smokers of 300 mg/day. This is compatible with CLO PM status (in our system of classification, an extremely PM). It is likely that inflammation which was associated with rapid titration, by releasing cytokines, further contributed to the inhibitory effects associated with valproate and obesity on CLO metabolism.

[h] The patient was readmitted to the hospital. Atrial fibrillation was treated with cardioversion twice, using digoxin and amiodarone. She was given 4 mg lorazepam intravenously to sedate her.

[i] Echocardiogram was described as compatible with myocarditis with no structural heart defects and ejection fraction of 55%–60%.

[j] Intravenous haloperidol 5 mg/day.

[k] Intravenous haloperidol 15 mg/day. After this the patient developed pneumonia which was associated with a respiratory arrest which led to a hypoxic brain injury. See the prior article (Cook et al., 2015) for details.

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A klozapin gyenge metabolizációja és a miokarditisz kapcsolata: új esettanulmányok elemzése a korábbi adatok tükrében

Bevezető: A klozapin-indukálta miokarditisz a klozapin metabolizációja szempontjából túl gyors titrálásra adott hiperszenzitivitási reakció eredménye lehet. Az obezitás, infekciók és inhibitorok (pl. valproát) gyenge metabolizáló státuszhoz (poor metabolizers, PM) vezethetnek. Cikkünkben a minimum terápiás dózis és a titrálás vizsgálatával azt a hipotézist teszteltük, hogy PM státusz miatt alakult ki klozapin-indukálta miokarditisz négy amerikai páciensnél. **Módszerek:** Egy előzetes vizsgálat alapján, amely kilenc török miokarditiszes esetet elemzett, vizsgáltuk, 1. a dózis-koncentráció görbét (C/D arány); 2. a 340ng/ml szérum koncentrációhoz szükséges minimum terápiás dózist (a MP státusz markere); és 3. a titrálási sebességet. **Eredmények:** Mind a négy páciensnél PM sátusz volt valószínűsíthető (a minimum terápiás dózis sorrendben 134, 84, 119 és 107mg/nap volt). A PM státuszhoz hozzájárulhatott 1. valproát az 1., 2. és 4.esetben; 2. obezitás és húgyúti infekció a 2. és 3. esetben; 3. obezitás és túl gyors titrálás a 4.esetben. A 3. esetnél, ahol az amerikai protokollnak megfelelő normál titrálás történt, genetikailag meghatározott gyenge metabolizáció valószínűsíthető. Ebben az utóbbi esetben klozapin-indukálta eozinofília és szisztémás szimptóma szindróma (DRESS) alakult ki 12.5mg klozapin/nap provokáló teszt hatására három hónappal később. Eredményeink egybehangzóak a kilenc török esetről közölt tanulmánnyal, mely szerint mind a kilenc esetben PM státusz volt igazolható (6 valproát, 4 obezitás, 1 infekció és 1 genetikai okok miatt). **Konklúzió:** További vizsgálatok szükségesek, amelyek klozapinszint-méréssel és a PM státusz vizsgálatával feltárhatják az összefüggést a klozapin-indukálta miokarditisz és az egyénre szabott titrálás hiánya között.

Kulcsszavak: eklozapin titrálás, klozapin mellékhatás, gyógyszer interakció, gyógyszerszint monitorozás, klozapin-indukálta miokarditisz, szkizofrénia, valproát