SUPPLEMENTARY MATERIAL

Valproate, obesity and other causes of clozapine poor metabolism in the context of rapid titration may explain clozapine-induced myocarditis: A re-analysis of a Turkish case series

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Supplementary Box S1 Clozapine-induced myocarditis as a drug hypersensitivity reaction

1. Crucial role of rapid titration
• We propose that clozapine-induced myocarditis is a hypersensitivity reaction associated with a titration which is too rapid for that specific patient.[2] • To establish that the titration is too rapid for a patient, one needs to consider that clozapine metabolism is influenced by genetics, sex and smoking, co-medication, presence/absence of obesity or inflammation[3] (Supplementary Box S2).
2. Hypersensitivity model can be simplified in 3 phases[3]
• In the first phase, suppose a titration is too fast for that specific patient, due to the psychiatrist being too aggressive and/or the patient's clozapine PM status; this leads to a clozapine-induced inflammation which releases cytokines. • In the second phase, a positive feedback loop develops and the cytokines inhibit CYP1A2, which is the main metabolic enzyme for clozapine metabolism, and other CYPs, thus further increasing the serum clozapine concentrations. • In the third phase, if the titration continues, the inflammation becomes complicated by the development of auto-antibodies, or other autoimmune mechanisms, which leads to myocarditis.
3. Clozapine-induced inflammation
• The initial symptom is usually a CRP elevation; then frequently fever develops. • In the third stage the local signs of inflammation become obvious leading most frequently to myocarditis. This is not the only manifestation; other local inflammations including serositis, pneumonitis, hepatitis, pancreatitis, nephritis or colitis can occur in the first two months of treatment during too-rapid titration.[4]

CRP: c-reactive protein; CYP1A2: cytochrome P450 1A2; PM: poor metabolizer

Supplementary Box S2 Clozapine PMs

0. Defining clozapine PMs

- As clozapine is mainly metabolized by CYP1A2,[3] it follows the same pattern as other CYP1A2 drugs, with need for lower doses in female non-smokers and higher in male smokers. Tobacco smoking is an inducer while estrogens are inhibitors.
- After controlling for smoking and sex, Asians and their descendants, the Amerindians[5], have lower CYP1A2 activity so they need lower clozapine doses than non-Asians.
- In people with European ancestry, for clozapine dosing to reach the serum therapeutic concentration of 350 ng/ml, the approximate range is:[6]
  - 250 mg/day in female non-smokers (C/D ratio = 1.48 ng/ml per mg/day[a]) to
  - 400 mg/day in male smokers (C/D ratio = 0.95 ng/ml per mg/day.[b]
- We used the stratified values per sex and smoking in people of European ancestry to define clozapine PMs in our Turkish sample, who presumably had the same DNA ancestry.

1. Genetic clozapine PMs[7]

- In other CYPs, genetic PM status is identified in patients with no CYP activity who have 2 null alleles with no production of that CYP. In CYP1A2 there are no good studies of the prevalence of PMs across ancestry groups and insufficient knowledge of which CYP1A2 alleles have no activity, or so little activity, that it can be associated with PM status. CYP1A2 activity is confounded by environmental and personal variables, complicating genetic studies
- There is no understanding of why Asians/Amerindians may have lower CYP1A2 activity than people of European ancestry.
- Genetic clozapine PMs are probably relatively rare (<10-15% of patients) and are probably explained by relatively rare CYP1A2 mutations which may vary according to ancestry groups.
- In patients of European ancestry, two CYP1A2 alleles may be relevant:
  - CYP1A2*7 in heterozygous state is present in <0.1% of them. It was found in the first genetic clozapine PM. This French non-smoking woman had a clozapine C/D ratio=4.32 needing 81 mg/day of clozapine to reach the therapeutic concentration of 350 ng/ml. If some CYP1A2 was present and the effects of estrogens and smoking are the same as in average patients, a male smoker with the same allele may need 119 mg/day.[c]
  - CYP1A2*6 is a missense variant associated with lack of CYP1A2 activity present in up to 0.9% of people of European ancestry. It has never been studied in clozapine patients.

2. Clozapine PMs due to co-medication with inhibitors

- Any strong (e.g., fluvoxamine) or moderate (oral contraceptives OC or high doses of caffeine intake) inhibitor can phenoconvert a patient to clozapine PM status.
- Valproate is frequently co-prescribed with clozapine and has been identified as a risk factor for myocarditis.[1,3] Valproate is a complex drug since for both olanzapine and clozapine valproate can be both an inducer and inhibitor and the predominance of one of these two effects can change over time in the same individual.[8] With clozapine, the current information suggests that valproate may be an inhibitor of clozapine and possibly an inducer of norclozapine. Induction takes several weeks to develop; thus, during titration valproate may behave as an inhibitor and contribute to the risk of clozapine-induced myocarditis.[8]

3. Clozapine PMs due to obesity

- In some patients, obesity may contribute to higher serum clozapine concentrations and PM status. Moreover, obesity decreases the clearance of other CYP1A2 drugs.[3]

4. Clozapine PMs due to inflammation present before starting clozapine

- Unidentified inflammation may contribute to the patient behaving as a clozapine PM. Adding a rapid titration may make the situation worse by adding clozapine-induced inflammation.[9]

C: concentration; C/D: concentration-to-dose; CYP1A2: cytochrome P450 1A2; D: dose; PM: poor metabolizers; TDM: therapeutic drug monitoring.

[a]In 6 samples of European Caucasians,[6] we found a clozapine C/D ratio of 1.48 ng/ml per mg/day in 218 female non-smokers. By dividing the minimum therapeutic C of 350 ng/ml by the clozapine C/D ratio we found a minimum therapeutic D=236 (350/1.48=236) which can be rounded to 250 mg/day.

[b]In 6 samples of European Caucasians,[6] we found a clozapine C/D ratio of 0.95 ng/ml per mg/day in 546 male smokers. By dividing the minimum therapeutic C of 350 ng/ml by the clozapine C/D ratio we found a minimum therapeutic D=368 (350/0.95=368) which can be rounded to 400 mg/day so that clinicians can remember the number.

[c]In patients with average clozapine metabolism, males had lower metabolism by a factor of 0.84 and smokers by a factor of 0.81.[3] Therefore, if we multiply 4.32 ng/ml per mg/day by 0.84 and by 0.81 we obtain 2.94 ng/ml per mg/day leading to a dose of 119 mg/day to reach 350 ng/ml (350/2.94=119).

Supplementary Box S3 Limitations

1. The study was designed for a different purpose
• This study was designed to establish the frequency of clozapine-induced myocarditis. After a sudden death in October 2015 due to clozapine-induced myocarditis (Case 1), the cardiac monitoring recommended by Ronaldson et al.[10] became routine practice for all patients initiated on clozapine. Thus, this case series reflects clozapine-induced inflammation identified between January 2011 and June 2018 and the use of the monitoring protocol from October 2015 to June 2018. Clozapine TDM was measured but was not described in the original articles.[11,12] The available TDM was interpreted using clozapine C/D ratios, as it was done in the re-analysis of cases of myocarditis in a New York hospital.[2] This retrospective analysis of clozapine TDM, which was done to establish that all 10 patients behaved as clozapine PMs, has at least the benefit that there was no bias when the data was collected. The Turkish authors[11,12] did not know that many years later the last author would ask for the clozapine TDM to analyze it.
2. Lack of TDM analyses in 62 controls without clozapine-induced myocarditis
• On the other hand, the 9 patients with myocarditis had significantly higher CRP and troponin.[11]
3. Lack of prior studies on the speed of the clozapine titration
• We had to develop a complex system to quantify the level of clozapine PM status, the speed of titration during the first and second weeks, and the level of final dosage for a specific patient. • This complex system is not for use in clinical practice; it was developed to retrospectively interpret these cases. Clinicians only need to use lower, slower and personalized titrations and this may prevent cases of clozapine-induced myocarditis.[14]
4. Lack of genotyping for Case 4
• Case 4 was not genotyped to establish that he was a genetic clozapine PM. Following the available information (Supplementary Box S2, section1), he should have been genotyped for CYP1A2*6 and CYP1A2*7, the only two known mutations in Europeans associated with low activity.
5. Lack of studies of clozapine metabolism in Turkish patients
• Turkish people are from the same DNA ancestry group as Europeans. As a matter of fact, we included Turkish patients (and other Western Asians) in the same clozapine titration as patients of European ancestry;[14] this is why we used control data on clozapine metabolism from patients of European ancestry. Clozapine TDM studies are needed in Turkish patients.
6. Lack of daily measures of CRP and troponin
• Following the protocol developed by Ronaldson et al.,[10] CRP and troponin were measured at baseline and on days 7, 14, 21 and 28. • Supplementary Table S1 shows that in all patients ↑ CRP was identified first and before ↑ troponin. The number of days between them ranged between 2 and 18 days but we cannot rule out that daily measures of CRP and troponin could have provided fewer days between the ↑ CRP in a patient and the subsequent ↑ troponin in that patient.
7. Lack of consideration of antipsychotic co-prescription
• Due to the limited space in the text, we could not comment on another possible risk factor for myocarditis that has recently been identified.[1] The co-prescription of quetiapine or olanzapine was significant in a logistic regression of >3000 myocarditis cases reported to VigiBase. • The quetiapine corrected OR was 2.83 (95% CI 1.82 to 4.40) for seriousness; the OR was 2.12 (95% CI 1.03 to 4.35) for fatal outcomes.[1] This may reflect a pharmacodynamic effect of quetiapine. • The olanzapine corrected OR was 1.90 (95% CI 1.35 to 2.68) for seriousness. This may reflect a pharmacokinetic effect. Olanzapine competitive inhibition of CYP1A2 may be relevant during enzyme saturation when inflammation is increasing and further inhibiting clozapine metabolism.

C/D: concentration-to-dose; CI: confidence interval; CRP: c-reactive protein; CYP1A2: cytochrome P450 1A2; OR: odds ratio; PM: poor metabolizers; TDM: therapeutic drug monitoring.

Supplementary Table S1 First day for ↑ CRP and other signs as well as diagnostic[a] information

		First day for ↑			First day for cardiac abnormalities				
Case	Age-sex-smoking	CRP[b]	ESR[c]	Fever[d]	Tachycardia[e]	Troponin[f]	Echocardiography	Autopsy	Stop day
1	65 yo ♀ unknown	12		N	N	14	Baseline: Other abnormality[g]	Y[h]	14
3	27 yo ♀ non-smoker	14	16	14	12	N	19: Normal	N	20
4	32 yo ♂ smoker	14	N	N	6	19	33: Normal (late)[i]	N	20
5	42 yo ♂ smoker	10	30	N	N	N	29: Normal (late)[i]	N	16
6	23 yo ♂ non-smoker	12	13	N	N	18	17: Normal	N	18
7	48 yo ♀ smoker	5	N	N	20	20	41: Normal (late)[i]	N	22
8	19 yo ♀ non-smoker	1	N	N	19 SVT	19	19: Pericardial effusion[j]	N	20
9	52 yo ♂ non-smoker	17	19	15	N	19	18: Other abnormality[k]	N	19
10	23 yo ♂ non-smoker	8	13	13	N	16	13: Pericardial effusion[j]	N	16
					Pancreatitis and hepatitis				
2	29 yo ♀ smoker	18	14	N	N	14	14: N	N	34

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; N: no; SVT: Supraventricular tachycardia; Y: yes; yo: years of age.

[a]Case 2 was diagnosed with clozapine-induced hepatitis and pancreatitis. Nine other cases were diagnosed with clozapine-induced myocarditis: Case 1 was diagnosed through autopsy; the other cases had clinical myocarditis signs and symptoms and troponin >2 upper limit range or CRP >100 mg/L.

[b]Hospital CRP normal range is 0-0.8 mg/dL. Any value >0.8 was considered abnormal. We cannot rule out that CRP was elevated earlier than when described since there were no daily CRPs.

[c]Hospital ESR normal range is 0-20 mm/hour.

[d]Fever was considered T > 38^0C.

[e]Tachycardia is heart rate ≥ 120 bpm.

[f]The hospital troponin test varied in the middle of the study. In the beginning a Troponin-T level with a normal range of 0 – 0.04 ng/mL was used. Later a Troponine-1 test with a range of 14 - 42.9 pg/mL was used. Abnormal levels were defined using the range of the test used in each patient.

[g]It was normal for left ventricular systolic function although it showed left ventricular hypertrophy compatible with his hypertension.

[h]The patient was admitted due to an overdose of quetiapine and valproic acid. The autopsy provided a definitive diagnosis of myocarditis.

[i]Late means that the echocardiography was completed after the acute phase was over.

[j]The pericardial effusion was labeled as minimal.

[k]It was normal for left ventricular systolic function although it showed dilatation of the ascendant aorta.

Supplementary Table S2 CLO Cs and C/D ratios in this case series

Case	Age-sex-smoking	Obesity/ VPA	Day	Mean D (mg/day)	Concentrations (ng/ml)[a] CLO	NOR	Total	SS	Inflammation[c]	C/D ratio Total[d]	CLO[e]	D for 350 ng/ml	% therapeutic[b] 7 day[f]	14 day[f]
												Poor estimation[g]		
1	65 yo ♀ unknown	VPA	5	15[h]	42.5	16.5	59	N	Unknown	3.93	2.83	124	40%	101%
3	27 yo ♀ non-smoker	VPA	12	90[i]	223	98	321	N	Unknown	3.57	2.48	141	53%	106%
4	32 yo ♂ smoker	none	16	95[j]	236	76	312	N	Y[k]	3.28	2.48	141	35%	71%
5	42 yo ♂ smoker	VPA	10	70[l]	94.8	34.2	129	N	Y[m]	1.84	1.35	260	29%	96%
6	23 yo ♂ non-smoker	obese	9	125[n]	284	118	402	N	N	3.22	2.27	154	97%	195%
			18	350[o]	767	337	1104	N	Y[p]	3.15	2.19	160	94%	188%
7	48 yo ♀ smoker	obese	8	70[l]	294	111	405	N	Y[q]	5.79	4.20	83	120%	301%
			14	190[r]	946	354	1300	N	Y[s]	6.84	4.98	70	143%	357%
			20	300	1693	604	2297	Y	Y[t]	7.66	5.64	62	161%	403%
8	19 yo ♀ non-smoker ↑ CRP before CLO UTI later diagnosed[w]	both	14	120[u]	323	116	439	N	Y[v]	3.66	2.69	130	38%	154%
9	52 yo ♂ non-smoker	VPA	14	90[i]	273	117	390	N	Unknown	4.33	3.03	116	65%	129%
10	23 yo ♂ non-smoker	VPA	14	190[y]	924	138	1062	N	Y[z]	5.59	4.86	72	139%	208%
2	29 yo ♀ smoker	obese	13	180[aa]	739	281	1020	N	Unknown	5.67	4.11	85	88%	353%

C: concentration; C/D: concentration-to-dose; CLO: clozapine; CRP: c-reactive protein; D: dose; N: no; NORC: norclozapine; SS: steady-state; TDM: therapeutic drug monitoring; UTI: urinary tract infection; VPA: valproate; Y: yes; yo: years of age.

[a]The TDM data has never been published. Approximately 5 ml of venous blood was collected in heparin-coated tubes at trough state before taking the medication (between 7:00 am – 9:00 am and about 12 h after the last clozapine intake). The samples were centrifuged, the serum separated and stored at -20°C until assayed which was performed within a week. The concentration of clozapine and norclozapine was determined by using high-performance-liquid-chromatography coupled with ultraviolet detection (the Shimadzu Prominence device of Rotakim Analysis Services and Technical Equipment Company).

[b]D needed to reach CLO concentration of 350 ng/ml. It is calculated by dividing 350/CLO C/D ratio. Steady state was defined as at least 5 days without any clozapine dosing changes (5 half-lives of 24 hours).[3] During titration for clinical practice it is not easy to keep dosing unchanged for 5 days, so in the case of concentrations that were not stable for 5 days, the mean dose of the last 5 days was used as an approximation to calculate the mean clozapine and total C/D ratios, as in prior studies.[2,9]

[c]Inflammation reflects whether C was contaminated or not by inflammation on the day it was collected.

[d]The total clozapine C/D ratio in ng/ml per mg/day was calculated by dividing the total serum concentration (clozapine and norclozapine) by the dose as an additional measure of clozapine clearance. The total C was calculated by adding CLO and NORC Cs.

[e]The clozapine C/D ratio in ng/ml per mg/day was calculated by dividing the trough serum concentration by the dose. It is the most important measure of clozapine clearance.

[f]% of D needed to reach 350 ng/ml that was reached at day 7 and day 14 of the titration. It is calculated by dividing the D at day 7 (or 14) of the titration of that specific patient (described in Table 1) by the therapeutic D needed for 350 ng/ml in the prior column to the left.
[g]To estimate the D for 350 ng/ml, we assume that the CLO C/D ratio in the individual is constant unless there is a change in confounding variable and CLO metabolism follows linear kinetics. CLO appears to follow linear kinetics in therapeutic concentrations, but when serum CLO Cs are <150 ng/ml,[3] CLO may not follow linear kinetics. This means that estimations of a D for 350 ng/ml based on results using very low CLO Cs tend to provide poor estimations.
[h]The daily Ds on the prior 5 days were 0-12.5-12.5-25-25. The mean D on the prior 5 days was 15 mg/day.
[i]The daily Ds on the prior 5 days were 75-75-100-100-100. The mean D on the prior 5 days was 90 mg/day.
[j]The daily Ds on the prior 5 days were 75-100-100-100-100. The mean D on the prior 5 days was 95 mg/day.
[k]On day16, the CLO concentration was associated with ↑ CRP to 0.915 mg/dL.
[l]The daily Ds on the prior 5 days were 50-50-75-75-100. The mean D on the prior 5 days was 70 mg/day.
[m]On day 10, the CLO concentration was associated with ↑ CRP to 1.05 mg/dL.
[n]The daily Ds on the prior 5 days were 75-100-125-150-175. The mean D on the prior 5 days was 125 mg/day.
[o]The daily Ds on the prior 5 days were 300-300-350-400-400 mg. The mean D on the prior 5 days was 350 mg/day.
[p]On day 18, the CLO concentration was associated with ↑ CRP to 10.01 mg/dL and had been ↑ for at least 6 days.
[q]On day 8, the CLO concentration was associated with ↑ CRP to 1.74 mg/dL and had been ↑ for at least 3 days.
[r]The daily Ds on the prior 5 days were 150-150-200-200-250 mg. The mean D on the prior 5 days was 190 mg/day.
[s]On day 14. the CLO concentration was associated with ↑ CRP to 2.88 mg/dL and had been ↑ for at least 9 days.
[t]On day 20, the CLO concentration was associated with ↑ CRP to 12 mg/dL and had been ↑ for at least 15 days.
[u]The daily Ds on the prior 5 days were 100-100-100-150-150. The mean D on the prior 5 days was 120 mg/day.
[v]On day 14, the CLO concentration was associated with ↑ CRP to 0.859 mg/dL. CRP had been elevated since the first day of CLO.
[w]On day 1 the medical chart reported no symptoms of infection or inflammation but a UTI was diagnosed on day 15. We suspect that the UTI was present from day 1 and was not diagnosed since symptoms were not present.
[y]The daily Ds on the prior 5 days were 150-175-200-225-200. The mean D on the prior 5 days was 190 mg/day.
[z]On day14, the CLO concentration was associated with ↑ CRP, which was likely since the day before it was 2.98 mg/dL and after it was 4.32 mg/dL. CRP had been ↑ for at least 6 days.
[aa]The daily Ds on the prior 5 days were 100-200-200-200-200. The mean D on the prior 5 days was 180 mg/day.

Supplementary Table S3 Data used to build Table 2

PM		Titration increase		Overdose[a]
Risk factors	Severity[b]	Rapidity - First week (0 to 7)[c]	Rapidity - Second week (7 to 14)[d]	final vs therapeutic dose
1: VPA(non-smoker)[e]	Mild (0.53=124/236)	40% (0 to 40%)	Mild 61% (40 to 101%)	Mild (1.01) 125 vs 124 mg/d
(smoker)[e]	PM (0.35=124/357)	40% (0 to 40%)	Mild 61% (40 to 101%)	Mild (1.01) 125 vs 124 mg/d
3: VPA	PM (0.60=141/236)	Mild 53% (0 to 53%)	34% (53 to 87%)	Mild (1.40) 200 vs 141 mg/d
4: None known	PM (0.38=141/368)	35% (0 to 35%)	36% (35% to 71%)	(0.87) 125 vs 141 mg/d
5: VPA	Mild (0.71=260/368)	29% (0 to 29%)	Mild 67% (29% to 96%)	(0.96) 250 vs 260 mg/d
6: Obesity[f]	Mild (0.60=154/256)	Rapid 97% (0 to 97%)	Mild 98% (97% to 195%)	Very (2.60): 400 vs 145 mg/d
7: Obesity[g]	Extreme (0.23 (83/357)	Very 120% (0 to 120%)	Very 181% (120% to 301%)	Extreme (3.61) 300 vs 83 mg/d
8: VPA + obesity	PM (0.55=130/236)			
UTI	Inflammation	38% (0 to 38%)	Rapid 116% (38% to 154%)	High (1.54) 200 vs 130 mg/d
9: VPA	PM (0.45=116/256)	Mild 65% (0 to 65%)	Mild 64% (65% to 129%)	Mild (1.29) 150 vs 116 mg/d
10: VPA + obesity	Extreme (0.28=72/256)	Mild 65% (0 to 139%)	Mild 69% (139% to 208%)	Very (2.08) 150 vs 72 mg/d
2: Obesity	Extreme (0.24=85/357)	Rapid 88% (0 to 88%)	Extreme 265% (88% to 353%)	Extreme (3.53) 300 vs 85 mg/d

CLO: clozapine; PM: poor metabolizer; UTI: urinary tract infection; VPA: valproic acid.

[a]The ratio between the final dose and the minimum therapeutic dose was calculated. This ratio was used to classify the final dose as an overdose. A final dose which was 1.01-1.51-fold higher than the minimum therapeutic dose for that specific patient was mildly high; a dose 1.51-2.00 times higher than the minimum therapeutic dose for that specific patient was high; a dose between 2.01-3.00 times higher than the minimum therapeutic dose was very high; and a dose >3.00 times higher than the minimum therapeutic dose was extremely high.

[b]Severity refers to the severity of PM status. The mean dosage for European Caucasians based on their sex and smoking status was used as a comparison (368 mg/day for a ♂ smoker, 357 mg/day for a ♀ smoker, 256 mg/day for a ♂ non-smoker and 236 mg/day for a ♀ non-smoker). A mildly PM was one who needed half to ¾ of the minimum therapeutic dose of an average European with the same sex and smoking status. A clozapine PM patient only needed half, but >1/4, of the minimum therapeutic dose for an average European with the same sex and smoking status. A very PM case needed <¼ of the minimum therapeutic dose of the stratified group for an average European with the same sex and smoking status.

[c]A titration between 41-80% of the minimum therapeutic dose for that specific patient was mildly rapid, a titration between 81-120% was rapid, and a titration >120% was very rapid.

[d]A titration between 61-120% of the minimum therapeutic dose for that specific patient was mildly rapid, a titration between 120-180% was rapid, a titration between 181-240% was very rapid and a titration >240% was extremely rapid.

[e]As smoking status was missing, both values are calculated.

[f]We had two CLO CD ratios: one from day 9 (2.27), not in steady state and unknown whether it was contaminated by inflammation, and another from day 18 (2.19) in steady state and contaminated by inflammation. None was ideal so we reflect here the more conservative option; the lower ratio (2.19) was used. If we had used 2.27 the titration would have been slightly faster.

[g]We had two CLO CD ratios: one from day 8 (4.20), not in steady state and unknown whether it was contaminated by inflammation, and another from day 20 (5.64) in steady state and contaminated by inflammation. Neither was ideal so we reflect here the more conservative option; the lower ratio (4.20) was used. If we had used 5.64, the titration would have been much faster.

Supplementary Table S4 Titrations from the book by Taylor et al.[13] transformed into percentages of the target therapeutic dose

Target therapeutic dose	♀ non-smoker (250 mg/day)	♂ non-smoker (350 mg/day)	♀ smoker (450 mg/day)	♂ smoker (550 mg/day)
Week 1:	0 to 100 mg/day	0 to 100 mg/day	0 to 100 mg/day	0 to 100 mg/day
% of target dose	0 to 40%	0 to 29%	0 to 22%	0 to 18%
Increase from day 0 to 7	40%[a]	29%	22%	18%
Week 2:	125 to 275 mg/day	125 to 275 mg/day	125 to 275 mg/day	125 to 275 mg/day
% of target dose	50 to 110%	36 to 79%	28% to 61%	23 to 50%
Increase from day 8 to 14	60%[b]	43%	33%	27%

[a]For our study, a titration between 41-80% of the therapeutic dose for that specific patient was mildly rapid, a titration between 81-120% was rapid, and a titration >120% was very rapid.

[b]For our study, a titration between 61-120% of the therapeutic dose for that specific patient was mildly rapid, a titration between 120-180% was rapid, a titration between 181-240% was very rapid and a titration >240% was extremely rapid.