Pharmacometric Modeling of Drug Adverse Effects: An Application of Mixture Models in Schizophrenia Spectrum Disorder Patients Treated with Clozapine

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Background: Clozapine

- Treatment of choice for TRS.[1]
- Minimize the risk of suicide.[2]
- Ameliorate the negative symptoms.[3]
- Clozapine have lower hospitalization and D/C, and improved CGI and symptoms vs AAP.[4]

1-Albitar et al., Pharm (2021).
2-DeBattista. Basic and Clinical Pharmacology (2017).
3-Englisch et al., Mens Sana Monographs (2012).
4-Masuda et al., JAMA Psychiatry (2019).

Background: Clozapine adverse effects

- Less EPS
- Clozapine is underutilized due to its adverse effects.[5,6]
- ANC monitoring is recommended weekly after clozapine initiation until 6 months.[7]

5-Iqbal et al., PLoS One (2020).
6-Martini et al., Psychiatry Res (2021).
7-Boazak et al., Clin Schizophr Relat Psychoses (2018).

Background: Adverse effects

- Adverse effects were historically classified[8]:
  - Type A: an exaggeration of drug actual pharmacological effects (thought to be dose-dependent).
  - Type B: not predictable by the drug pharmacological action (may be less related to the drug dose).

- Dose relatedness, timing, and patient susceptibility (DoTS) classification.[9]
  - **Do**se of the drug.
  - **T**ime course of the reaction.
  - **S**usceptibility factors.

8-Phillips. Br. J. Clin. Pharmacol (2016).
9-Aronson et al., Br. Med. J. (2003).

Methods: DoTS modeling

Dose

- Exposure-ADR modeling may be appropriate only for drugs administered based on the maximum tolerated dose.[8]

Time course

- Drug effect can be represented as a function of time in DP models, which describes the disease status using mathematical functions of disease severity biomarkers or clinical outcomes.[10]

Patient susceptibility

- Mixture model describes the multimodal distribution of a parameter.[11]

8-Phillips. Br. J. Clin. Pharmacol (2016).
10-Holford. Br J Clin Pharmacol (2015).
11-Carlsson et al., AAPS J (2009).

Methods: DoTS modeling

$$S(t) = S_0 + \alpha \times t + E[Ce(t)]$$

$$A(t) = A_0 + AE[Ce(t)]$$

$$A(t) = A_0$$

Methods: Base models

Time course	Function	Model
Symptomatic	Offset	$A(t) = \theta_{bsl}(1 + \theta_{offset})$
Progressive	Linear	$A(t) = \theta_{bsl}(1 + \theta_{SL} \times t)$
	Exponential	$A(t) = \theta_{bsl} + \theta_{max}(1 - e^{-\theta_{KAE} \times t})$
	Piecewise linear	$A(t) = \theta_{bsl} + \left(1 - \frac{t^{100}}{t^{100} + \theta_{SWT}{}^{100}}\right)\theta_{SL} \times t + (\theta_{SWT} \times \theta_{SL})\frac{t^{100}}{t^{100} + \theta_{SWT}{}^{100}}$
Transient	Inverse Bateman	$A(t) = \theta_{bsl}(1 - \theta_{AMP}\left(\frac{\theta_{KAE}}{\theta_{KAE} - \theta_{KRec}}\right)\left(e^{-\theta_{KAE} \times t} - e^{-\theta_{KRec} \times t}\right))$
	Surge	$A(t) = \theta_{bsl}\left(1 - \frac{\theta_{AMP}}{\left(\frac{t - \theta_{PT}}{\theta_{PW}}\right)^4 + 1}\right)$

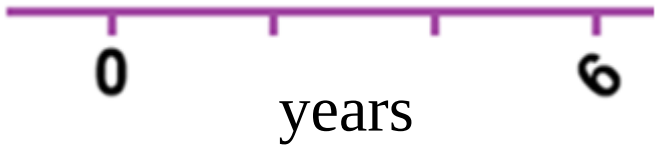
Methods: Combined model

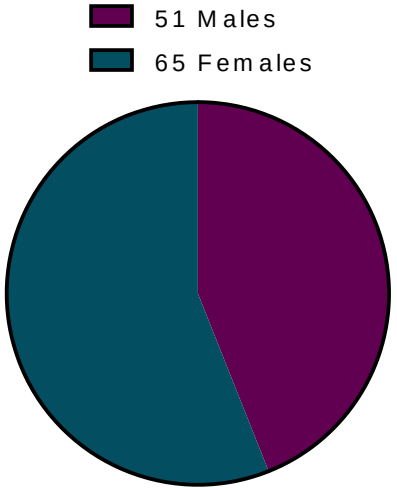
Subpopulation	Tachycardia	Weight gain	ANC drop
1	Yes	Yes	Yes
2	Yes	Yes	No
3	Yes	No	Yes
4	No	Yes	Yes
5	Yes	No	No
6	No	Yes	No
7	No	No	Yes
8	No	No	No

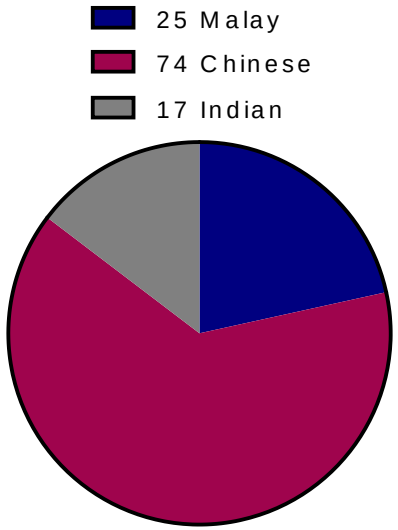
Results: Data

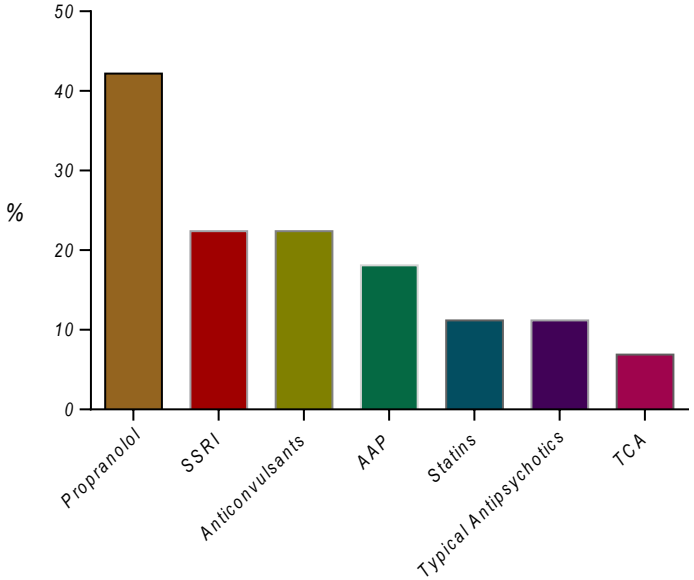
Hospital Pulau Pinang

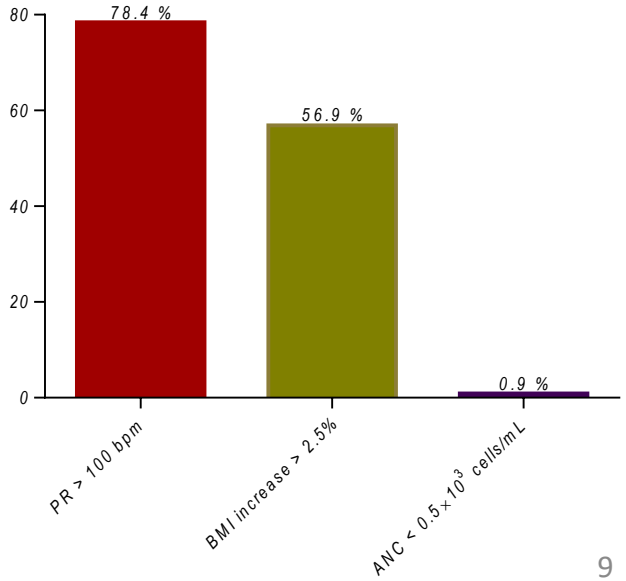
> 7000 observations



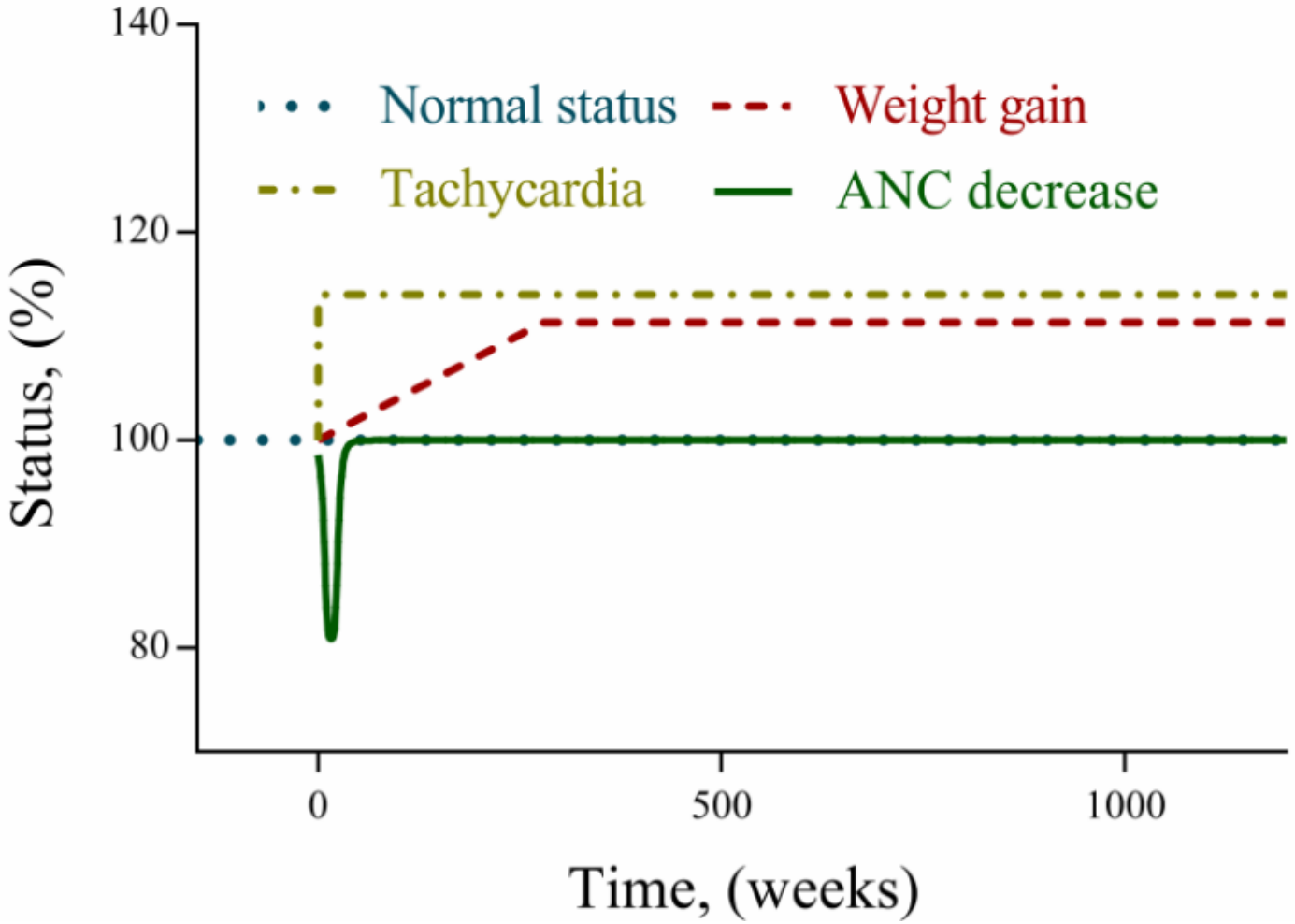








Results: Base models



Results: Combined model

Steps	NSP	Ref	Subpopulation estimates (RSE%)							
			AD+WG+TC	AD+WG	AD+TC	WG+TC	AD	WG	TC	ΔOFV
Stepwise elimination										
1	8	na	0.202	0.018	0.173	0.080	0.001	0.001	0.291	na
2	6	1	0.201 (62)	0.019 (494)	0.174 (64)	0.080 (108)	-	-	0.291 (63)	-0.04
3	5	2	0.219 (42)	-	0.173 (64)	0.082 (107)	-	-	0.289 (64)	+0.05
4	4	3	0.298 (29)	-	0.174 (160)	-	-	-	0.284 (114)	+0.06
5	**3**	**4**	**0.445 (25)**	-	-	-	-	-	**0.305 (58)**	**+3.75**
6	2	5	0.556 (28)	-	-	-	-	-	-	+4.75
Forward addition										
7	4	5	0.444	-	-	0.001	-	-	0.304	+0.01
8	4	5	0.443	0.001	-	-	-	-	0.305	+0.01
9	4	5	0.444	-	-	-	-	0.001	0.305	+0.01
10	4	5	0.334 (32)	-	-	-	0.093 (81)	-	0.374 (50)	+2.25

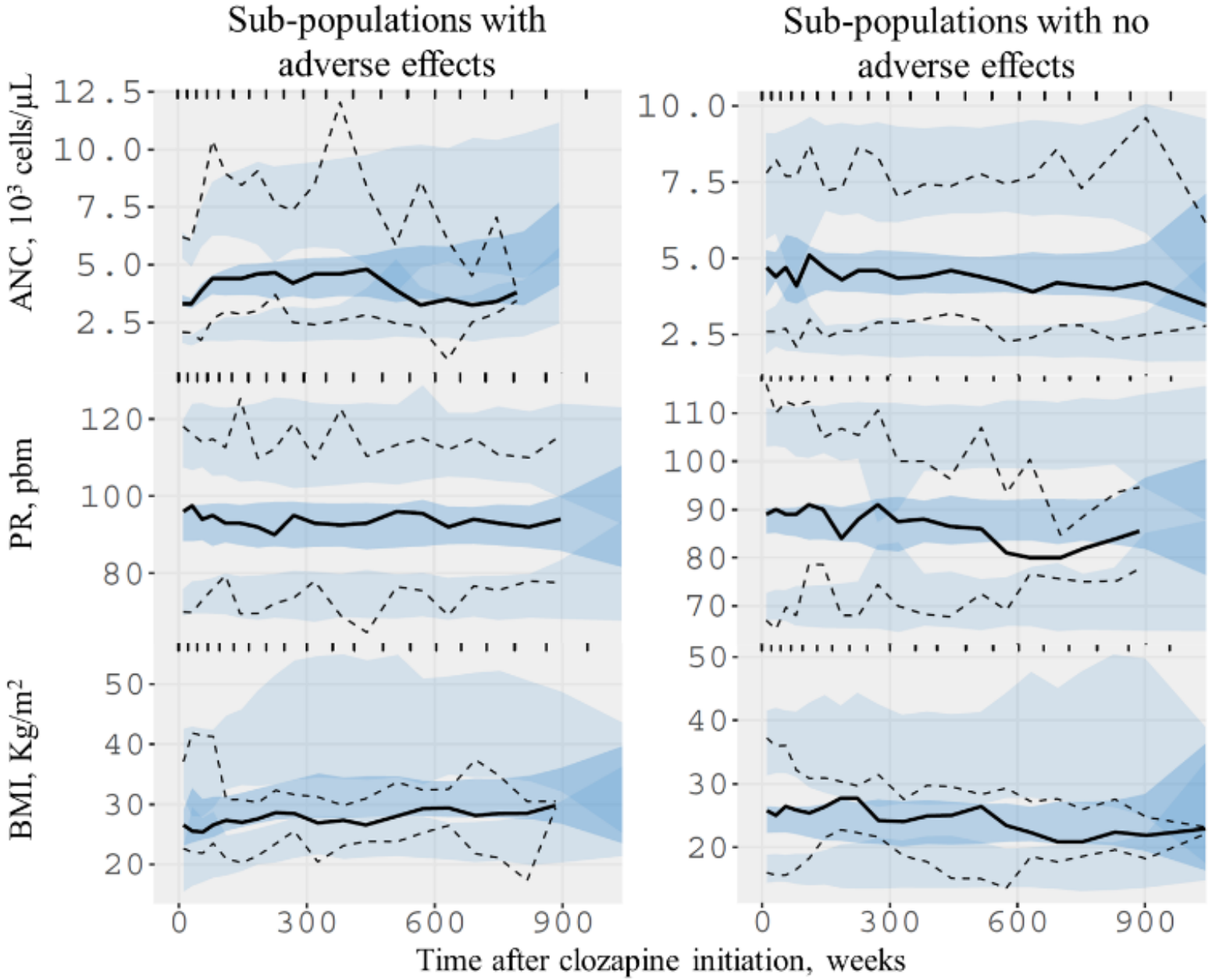
Results: Final model

BMI increase: 0.01 $Kg.m^{-2}.week^{-1}$ increase over a baseline of 24.7 $Kg.m^{-2}$ until reaching a plateau after 279 weeks.

ANC decrease: 20% from a baseline of 4540 $cells.\mu L^{-1}$ between week 12 and 20.8.

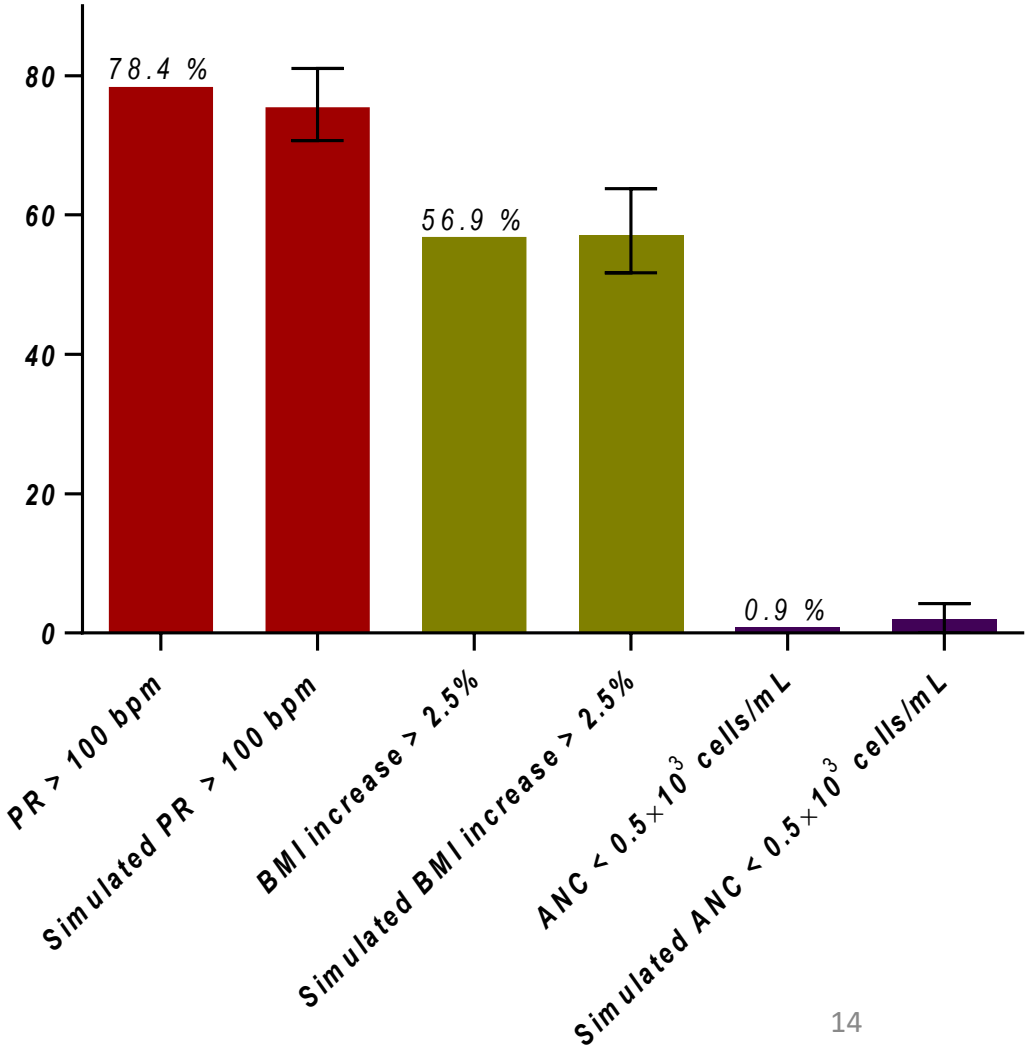
Tachycardia: 14% consistent increase over a baseline of 87.9 bpm corresponding to a 450 mg clozapine daily dose. Tachycardia increased to 20% with a clozapine daily dose of 600 mg.

Results: Mixture VPC



Results: Simulation exercise

	Observed	Simulated mean	Simulated 90% CI
PR > 100 bpm	78.4%	75.5%	70.7-81.0%
BMI increase > 2.5%	56.9%	57.2%	51.7-63.8%
ANC < 0.5×10^3 cells/mL	0.9%	1.9%	0-4.3%



Discussion: Model development

DP models: mathematical descriptions of the disease status as a function of time to better account for the drug effect.[12,13]
Predictors of baseline disease progression can be investigated.[14,15]

- Mixture model accounts for the multimodal distribution parameters such as the modeling of responders and non-responders in clinical trials with dose escalation design.[16]
- Mixture model was used to model ordered categorical adverse events data.[17]

12. Mould et al., Clin. Pharmacol Ther (2007).
13. Venuto et al., Mov Disord (2016).
14. Samtani et al., Br J Clin Pharmacol (2013).
15. Passey et al., J Clin Pharmacol (2015).
16. Shiiki et al., Pharm Res (2002).
17. Kowalski et al., J Pharmacokinet Pharmacodyn (2003).

Discussion: Weight gain

- Weight gain percentages18-60%.[5,6,18-23]
- Magnitude 3-15% after 3-12 months.[21,22]
- Steadily increase until it reaches a plateau after 189-207 weeks.[23,24]

- Predictors: Females;[22,25] smokers;[5,22] non-smokers;[26] younger age.[5,23]
- None predictors: Smokers;[27] Age;[22] Dose, concentrations, or metabolite.[22,28]

5. Iqbal et al., PLoS One (2020).
6. Martini et al., Psychiatry Res (2021).
18. Hyde et al., Curr Drug Saf (2015).
19. Schneider et al., Eur Psychiatry (2014).
20. Tso et al., Australas Psychiatry (2017).
21. Gressier et al., Eur Neuropsychopharmacol (2016).
22. Lau et al., J Clin Psychopharmacol (2016).
23. Bai et al., Schizophr Res (2009).
24. Henderson et al., Am J Psychiatry (2000).
25. Alberich et al., J Psychiatry Res (2019).
26. Gebhardt et al., J Psychiatr Res (2009).
27. Seppälä et al., Nord J Psychiatry (2014).
28. Simon et al., J Clin Psychiatry (2009).

Discussion: Neutropenia

- Severe neutropenia percentages 0.4-0.9%.[29,30]
- Mild neutropenia percentages 4-15%.[30,5,19]
- 84% of all neutropenia incidences within 5 months of clozapine exposure.[30]

- Predictors: Females;[31,32] concentration.[34]
- None predictors: Dose;[31,34] concentration;[33] Age.[22]

5. Iqbal et al., PLoS One (2020).
19. Schneider et al., Eur Psychiatry (2014).
22. Lau et al., J Clin Psychopharmacol (2016).
29. Li et al., Psychol Med (2020).
30. Myles et al., Acta Psychiatr Scand (2018).
31. Tunsirimas et al., Asian J Psychiatr (2019).
32. Hollingworth et al., Psychopharmacol (2018).
33. Smith et al., CNS Drugs (2017).
34. Willcocks et al., Frontiers in Pharmacology (2021).

Discussion: Tachycardia

- Tachycardia 10-55%.[5,6,18,19,35,36]
- Clozapine (107 bpm), haloperidol (86 bpm), olanzapine (89 bpm) vs control (62 bpm).[35]
- Not transient through 24 hours ambulatory ECG.[37]

- Beta-blockers are the main treatment.[35,37]
- Predictors: younger age;[5,18] smokers;[5] males.[6]

5. Iqbal et al., PLoS One (2020).
6. Martini et al., Psychiatry Res (2021).
18. Hyde et al., Curr Drug Saf (2015).
19. Schneider et al., Eur Psychiatry (2014).
35. Lally et al., Cochrane Database Syst. Rev (2016).
36. Nilsson et al., Int Clin Psychopharmacol (2017).
37. Nilsson et al., Schizophr Res (2018).

Advantages

Advantages

- Evaluation of dose exposure, time course, and patient susceptibility.
- Description of Adverse effects on a continuous scale.
- Avoid cut-off points that are inconsistent across the literature.[29]
- New drug development.

29-Li et al., Psychol Med (2020).

Acknowledgments

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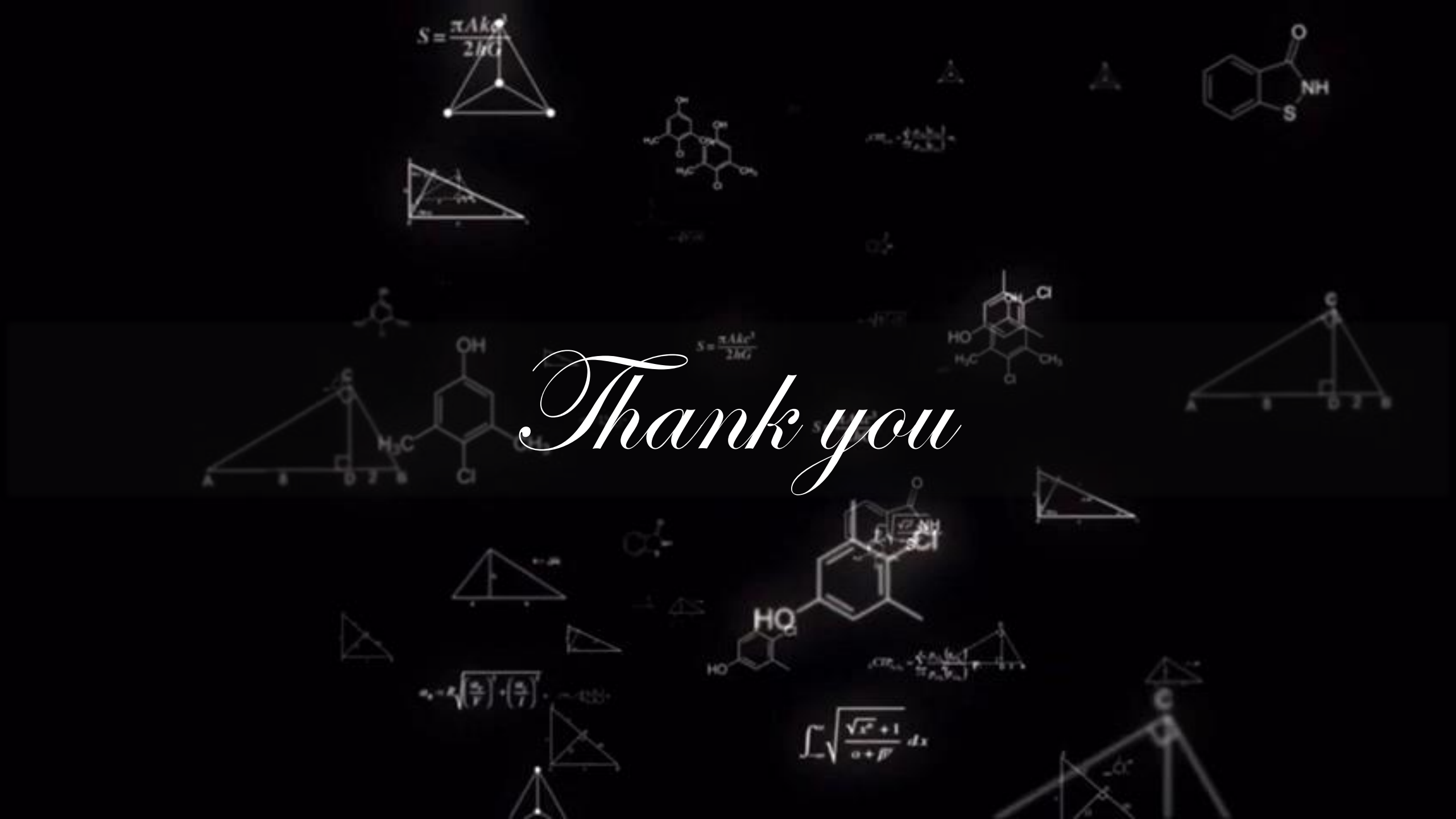
Thank you