Psychiatric Genetic Testing

CLOZAPINE PHARMACOGENTICS

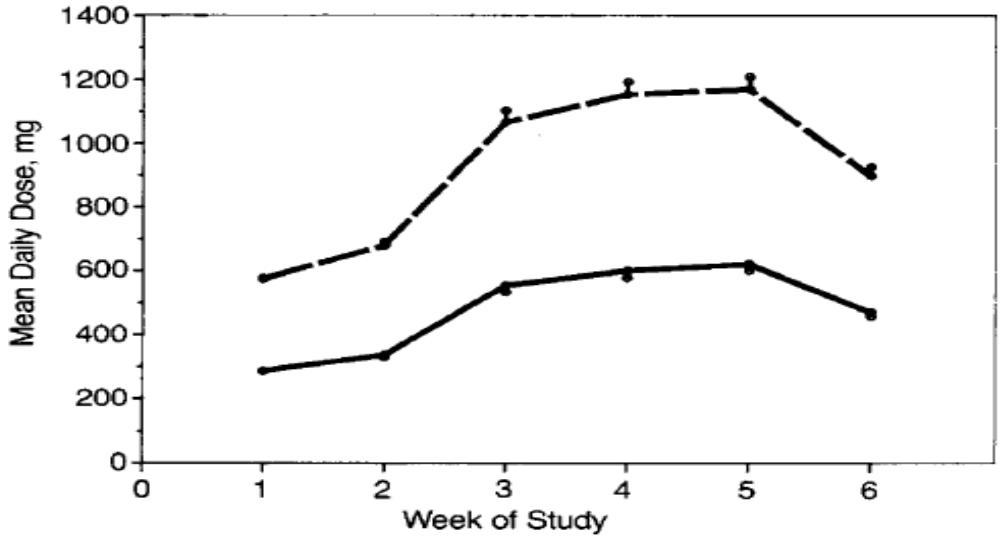


Fig 1.—Mean daily doses of clozapine (solid line) and chlorpromazine (broken line) during double-blind phase of study (period 4). For clozapine, at week 1, n = 126; week 2, n = 126; week 3, n = 122; week 4, n = 120; week 5, n = 119; and week 6, n = 116. For chlorpromazine, at week 1, n = 141; week 2, n = 140; week 3, n = 137; week 4, n = 133; week 5, n = 128; and week 6, n = 125.

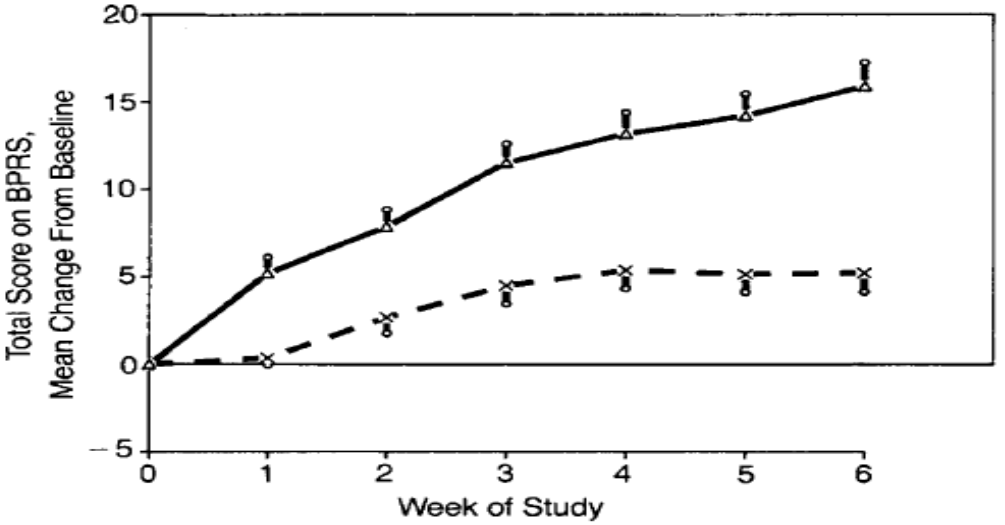


Fig 2.—Mean change from baseline in total score on Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztropine mesylate (broken line, n = 139). $P<.001$ during each week of study.

Table 6.—No. of Patients Whose Condition Improved*

Drug	No. (%) of Patients Whose Condition Improved	All Others, No. (%)	Total, No. (%)
Clozapine	38 (30)	88 (70)	**126 (100)**
Chlorpromazine	5 (4)	136 (96)	**141 (100)**
Total	**43** (16)	**224** (84)	**267 (100)**

*The categorization is based on the last evaluation completed for each patient. $P<.001$ by two-tailed Fisher's exact test.

Kane J, Honigfeld G, Singer J et al. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988; 45: 789-796

Acta Psychiatr Scand 2017: 1–15

DOI: 10.1111/acps.12742

ACTA PSYCHIATRICA SCANDINAVICA

International trends in clozapine use: a study in 17 countries

Bachmann CJ, Aagaard L, Bernardo M, Brandt L, Cartabia M, Clavenna A, Coma Fusté A, Furu K, Garuoliené K, Hoffmann F, Hollingworth S, Huybrechts KF, Kalverdijk LJ, Kawakami K, Kieler H, Kinoshita T, López SC, Machado-Alba JE, Machado-Duque ME, Mahesri M, Nishtala PS, Piovani D, Reutfors J, Saastamoinen LK, Sato I, Schuiling-Veninga CCM, Shyu Y-C, Siskind D, Skurtveit S, Verdoux H, Wang L-J, Zara Yahni C, Zoëga H, Taylor D. International trends in clozapine use: a study in 17 countries.

Objective: There is some evidence that clozapine is significantly underutilised. Also, clozapine use is thought to vary by country, but so far no international study has assessed trends in clozapine prescribing. Therefore, this study aimed to assess clozapine use trends on an international scale, using standardised criteria for data analysis.
Method: A repeated cross-sectional design was applied to data extracts (2005–2014) from 17 countries worldwide.
Results: In 2014, overall clozapine use prevalence was greatest in Finland (189.2/100 000 persons) and in New Zealand (116.3/100 000), and lowest in the Japanese cohort (0.6/100 000), and in the privately insured US cohort (14.0/100 000). From 2005 to 2014, clozapine use increased in almost all studied countries (relative increase: 7.8–197.2%). In most countries, clozapine use was highest in 40–59-year-olds (range: 0.6/100 000 (Japan) to 344.8/100 000 (Finland)). In youths (10–19 years), clozapine use was highest in Finland (24.7/100 000) and in the publicly insured US cohort (15.5/100 000).
Conclusion: While clozapine use has increased in most studied countries over recent years, clozapine is still underutilised in many countries, with clozapine utilisation patterns differing significantly between countries. Future research should address the implementation of interventions designed to facilitate increased clozapine utilisation.

C. J. Bachmann[1], L. Aagaard[2], M. Bernardo[3], L. Brandt[4], M. Cartabia[5], A. Clavenna[5], A. Coma Fusté[6], K. Furu[7], K. Garuoliené[8,9], F. Hoffmann[10], S. Hollingworth[11], K. F. Huybrechts[12], L. J. Kalverdijk[13], K. Kawakami[14], H. Kieler[4], T. Kinoshita[14], S. C. López[15], J. E. Machado-Alba[15], M. E. Machado-Duque[15], M. Mahesri[12], P. S. Nishtala[16], D. Piovani[5], J. Reutfors[4], L. K. Saastamoinen[17], I. Sato[14], C. C. M. Schuiling-Veninga[18], Y.-C. Shyu[19,20,21], D. Siskind[22], S. Skurtveit[7], H. Verdoux[23], L.-J. Wang[24], C. Zara Yahni[6], H. Zoëga[25], D. Taylor[26,27]

[1]Freelance Researcher, Marburg, Germany, [2]Life Science Team, Bech-Bruun Law Firm, Copenhagen, Denmark, [3]Barcelona Clinic Schizophrenia Unit, Neuroscience Institute, and Hospital Clínic, Department of Medicine, Barcelona University, and Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain, [4]Centre for Pharmacoepidemiology, Department of Medicine, Solna, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, [5]Pharmacoepidemiology Unit, Department of Public Health, IRCCS Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy, [6]Pharmacy Department of Barcelona Health Region, Catalan Health Service (CatSalut), Barcelona, Spain, [7]Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway, [8]Medicines Reimbursement Department, National Health Insurance Fund of the Republic of Lithuania, [9]Faculty of Medicine, Department of Pathology, Forensic Medicine and Pharmacology, Vilnius University, Vilnius, Lithuania, [10]Department of Health Services Research, Carl von Ossietzky University Oldenburg, Oldenburg, Germany, [11]School of Pharmacy, University of Queensland, Woolloongabba, Qld, Australia, [12]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [13]University of Groningen, University Medical Center Groningen, Department of Psychiatry, the Netherlands, [14]Department of Pharmacoepidemiology and Clinical Research Management, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan, [15]Grupo de Investigación en Farmacoepidemiología y

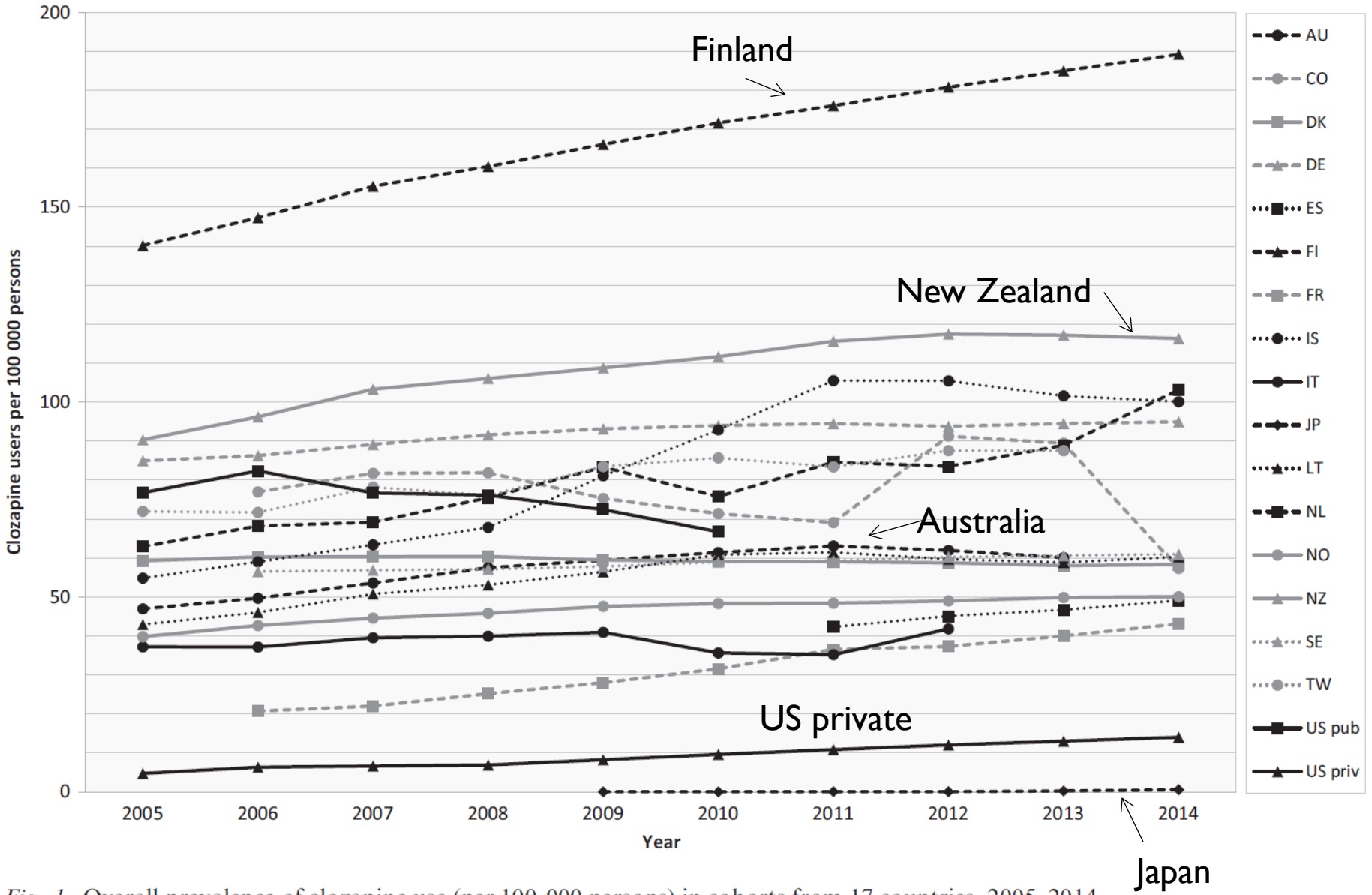


Fig. 1. Overall prevalence of clozapine use (per 100 000 persons) in cohorts from 17 countries, 2005–2014.

DOI: 10.1111/acps.13280

Acta Psychiatrica Scandinavica WILEY

ORIGINAL ARTICLE

An evaluation of the variation and underuse of clozapine in the United Kingdom

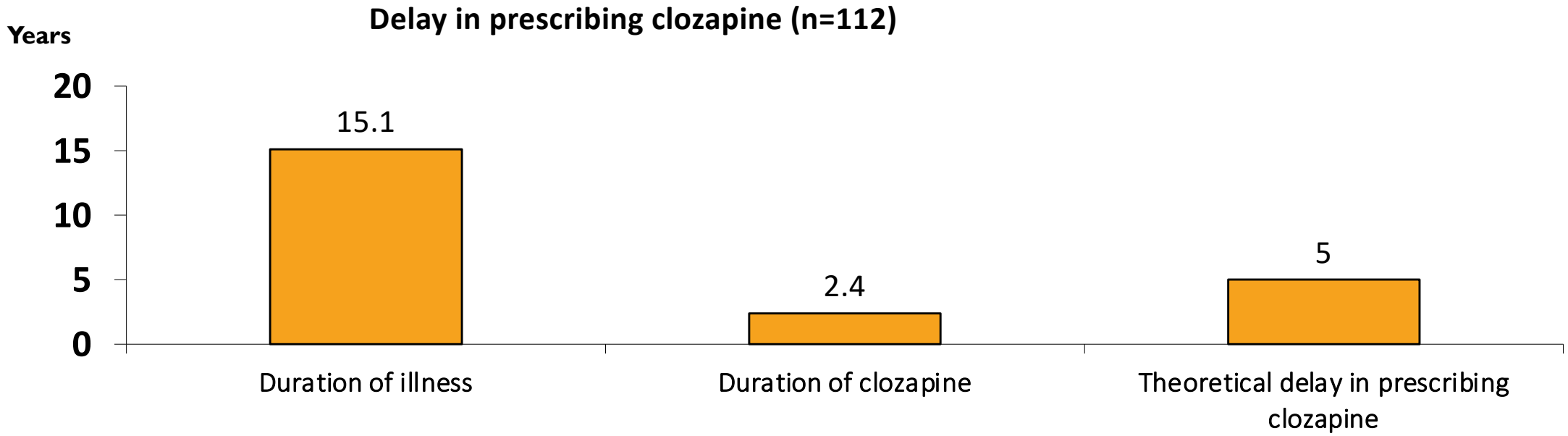
Eromona Whiskey[1,2,3] | **Alex Barnard**[4] | **Ebenezer Oloyede**[1,2,3] | **Olubanke Dzahini**[1,2] | **David M. Taylor**[1,2] | **Sukhwinder S. Shergill**[3]

Acta Psychiatr Scand. 2021;00:1–9.

Country	Clozapine prescription per 100,000 persons
Finland	189
Netherlands	103
Iceland	100
Germany	95
United Kingdom	69
Sweden	61
Denmark	58
Norway	50
Spain	49
France	43
Italy	42

NHS England Regional Office Name	Key (see map)	Clozapine prescription per 100,000 population	SMI prevalence per 100,000 population	Prescription % per prevalence
NHS England London	12	66.57	1,080.57	6.16%
NHS England North West (Cheshire and Merseyside)	5	62.40	1,039.68	6.00%
NHS England Midlands (North Midlands)	6	39.97	804.63	4.97%
NHS England Midlands (West Midlands)	8	72.60	567.16	12.80%
NHS England North West (Greater Manchester)	4	82.71	1,005.70	8.22%
NHS England North West (Lancashire and South Cumbria)	2	65.34	1,048.19	6.23%
NHS England South East (Hampshire, Isle of Wight and Thames Valley)	11	40.78	548.94	7.43%
NHS England South East (Kent, Surrey and Sussex)	13	41.38	838.70	4.93%
NHS England South West (South West North)	10	35.90	478.79	7.50%
NHS England South West (South West South)	14	43.80	898.01	4.88%
NHS England Midlands (Central Midlands)	7	43.86	816.48	5.37%
NHS England East of England (East)	9	35.26	821.72	4.29%
NHS England North East and Yorkshire (Cumbria and North East)	1	53.58	935.75	5.73%
NHS England North East and Yorkshire (Yorkshire and Humber)	3	37.56	719.60	5.22%

WHY?



PRIOR ANTIPSYCHOTIC PRESCRIBING IN PATIENTS CURRENTLY RECEIVING CLOZAPINE - A CASE NOTE REVIEW

Taylor D, Young C, Paton C. (2003) ***Journal of Clinical Psychiatry****, 64, 30-38*

Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation†

Oliver D. Howes,* Francis Vergunst,* Siobhan Gee, Philip McGuire, Shitij Kapur and David Taylor

Background
Clozapine is the only antipsychotic drug licensed for treatment-resistant schizophrenia but its use is often delayed. Since previous studies, national guidelines on the use of clozapine and other antipsychotics have been disseminated to clinicians.

Aims
To determine the theoretical delay to clozapine initiation and to quantify the prior use of antipsychotic polypharmacy and high-dose antipsychotic treatment.

Method
Clinico-demographic data were extracted from the treatment records of all patients commencing clozapine in our centre between 2006 and 2010.

Results
Complete records were available for 149 patients. The mean theoretical delay in initiating clozapine was 47.7 months (s.d. = 49.7). Before commencing clozapine, antipsychotic polypharmacy and high-dose treatment was evident in 36.2 and 34.2% of patients respectively. Theoretical delay was related to illness duration ($\beta = 0.7$, $P < 0.001$) but did not differ by gender or ethnicity.

Conclusions
Substantial delays to clozapine initiation remain and antipsychotic polypharmacy and high doses are commonly used prior to clozapine, despite treatment guidelines.

Declaration of interest
D.T. has received consultancies fees, lecturing honoraria and/or research funding from AstraZeneca, Janssen-Cilag, Servier, Sanofi-Aventis, Lundbeck, Bristol-Myers Squibb (BMS), Novartis, Eli Lilly and Wyeth. O.D.H. has been a speaker at meetings organised by and/or received investigator-initiated charitable research funding from Astra-Zeneca, BMS, Eli Lilly, and Jansenn-Cilag. S.K. has received grant support from AstraZeneca and GSK, and has served as consultant and/or speaker for AstraZeneca, Bioline, BMS-Otsuka, Eli Lilly, Janssen (J&J), Lundbeck, NeuroSearch, Pfizer, Roche, Servier and Solvay Wyeth.

REASONS FOR DELAYING CLOZAPINE

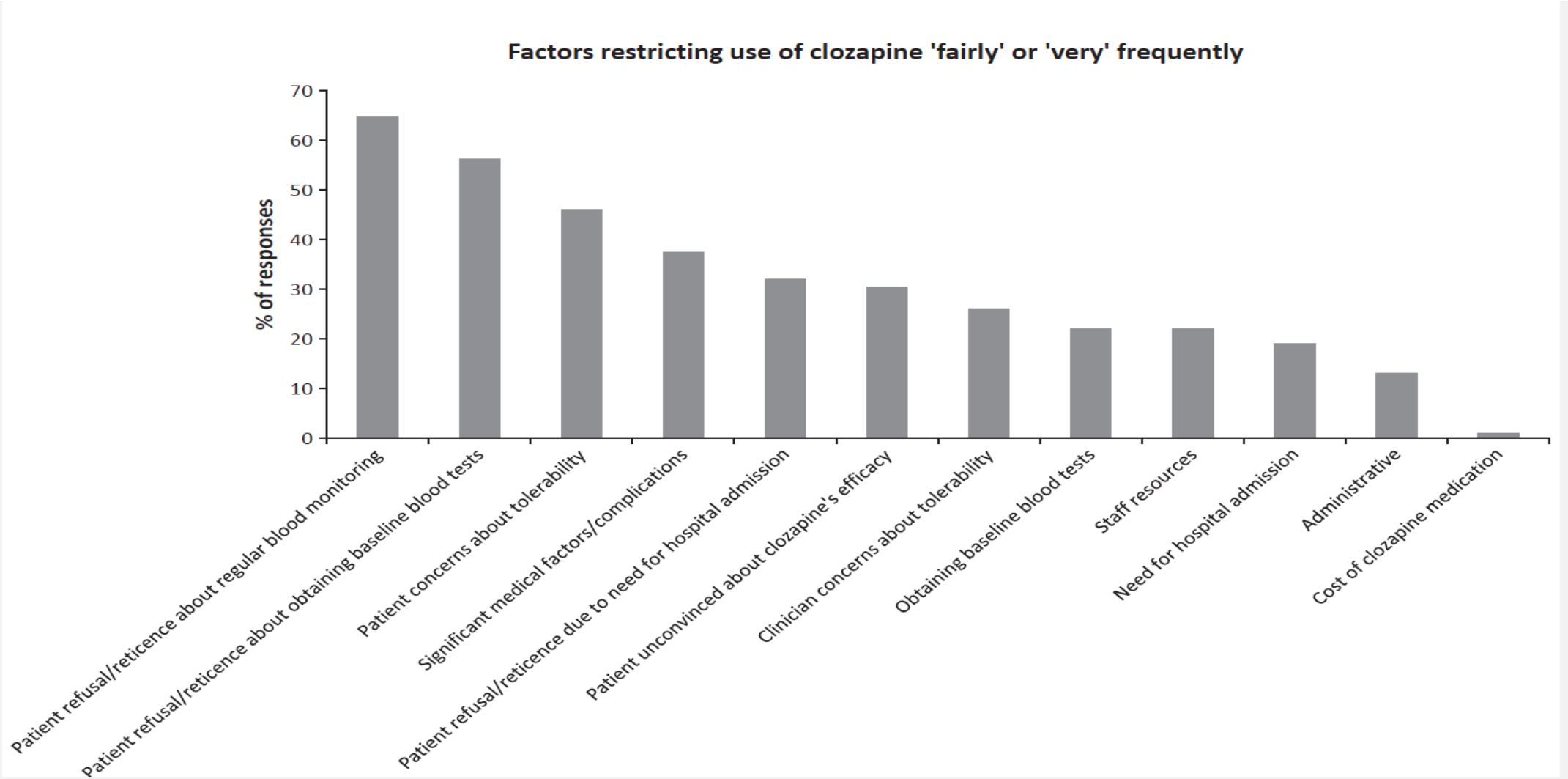
Acta Psychiatr Scand 2014: 130: 16–24

DOI: 10.1111/acps.12193

ACTA PSYCHIATRICA SCANDINAVICA

S. Gee[1,2], F. Vergunst[3,4], O. Howes[3], D. Taylor[1,2]

Practitioner attitudes to clozapine initiation



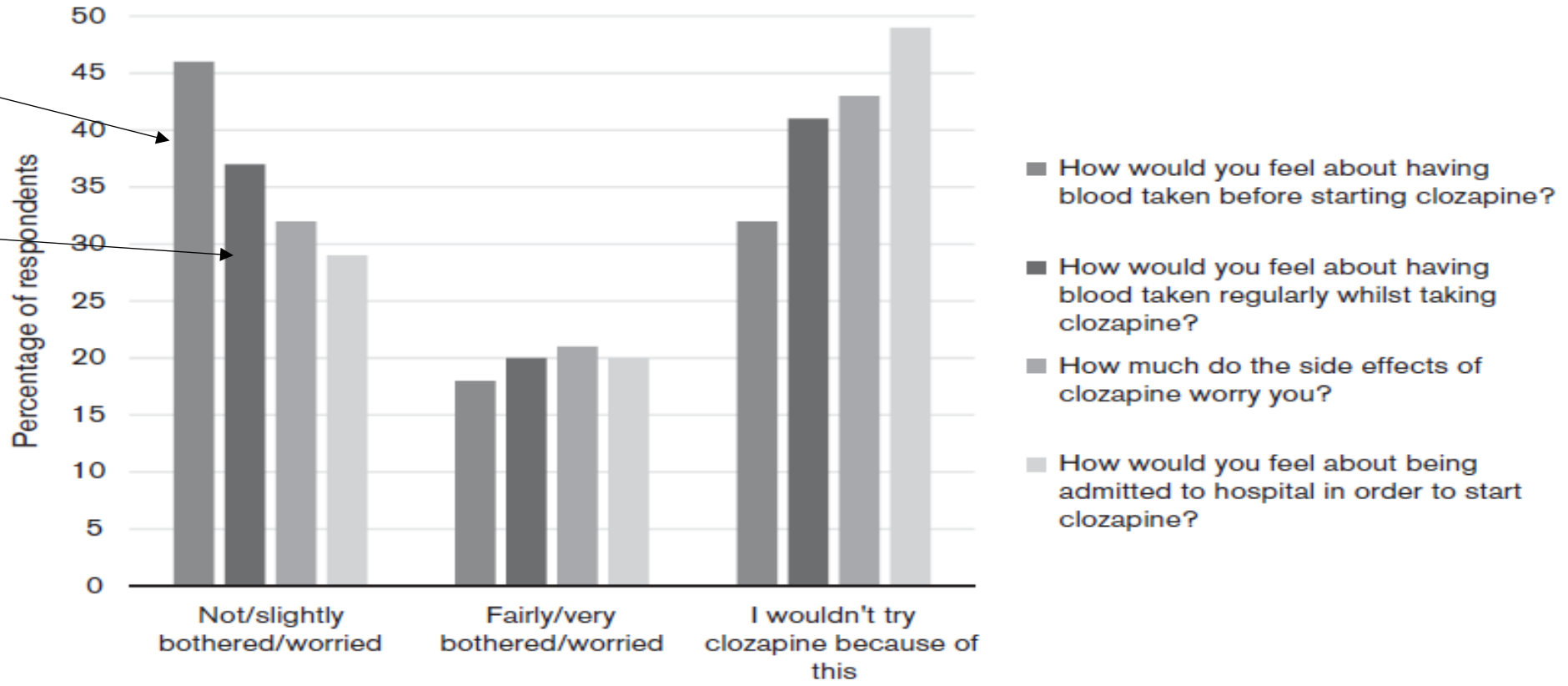
International Clinical Psychopharmacology 2017, 32:337–342

Patient attitudes to clozapine initiation

Siobhan H. Gee[a], Sukhwinder S. Shergill[b] and David M. Taylor[c]

Baseline bloods

Regular bloods



Responses to questionnaire, shown as percentage of responses for each question.

CLOZAPINE - PATIENT PERCEPTIONS

TAYLOR ET AL (2000) PSYCH BULL, 24: 450-452

N = 570/1284

UK

27 centres

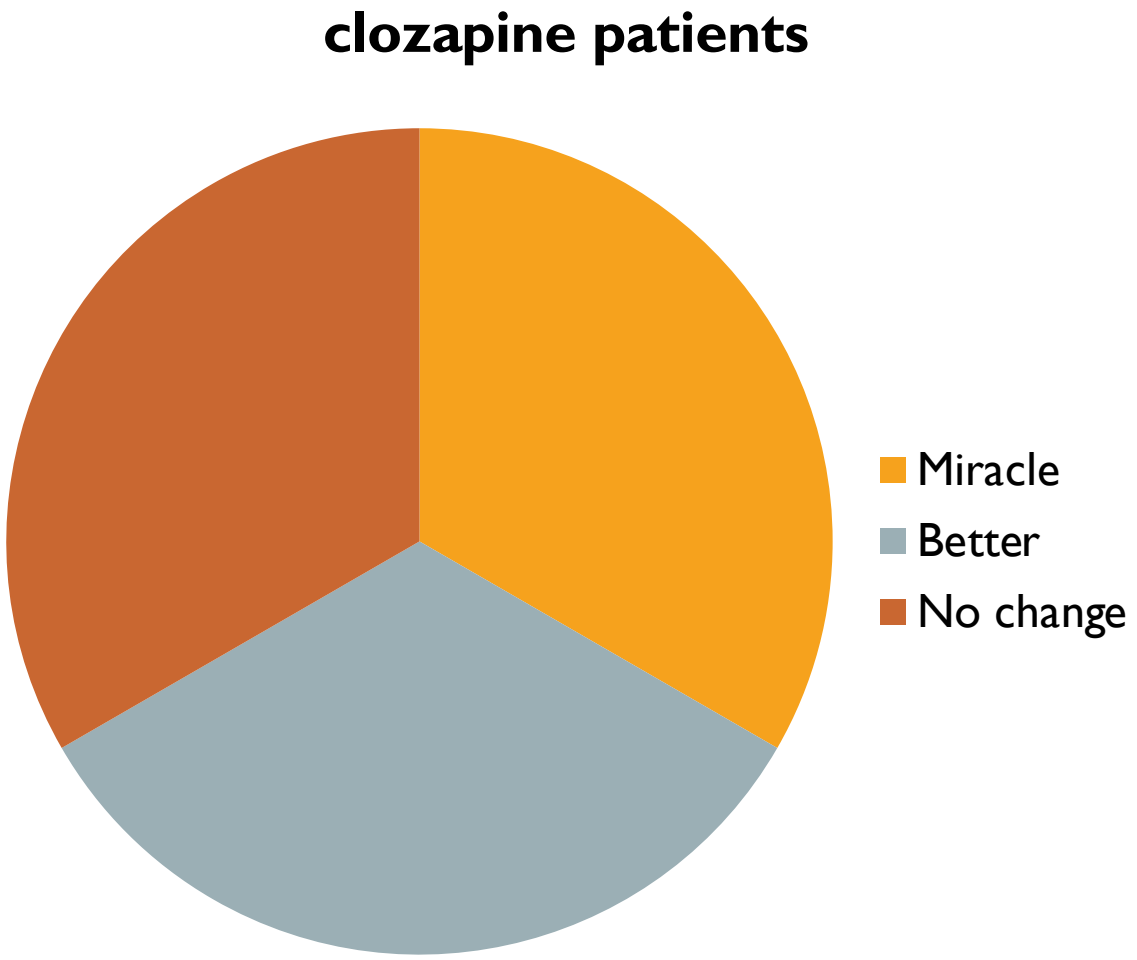
85% on clozapine for >6 months

	Yes	**No**
Feel better on clozapine	86.1%	12.5%
Advantages > disadvantages	87.0%	6.5%
Prefer clozapine to previous T_x	88.6%	6.5%

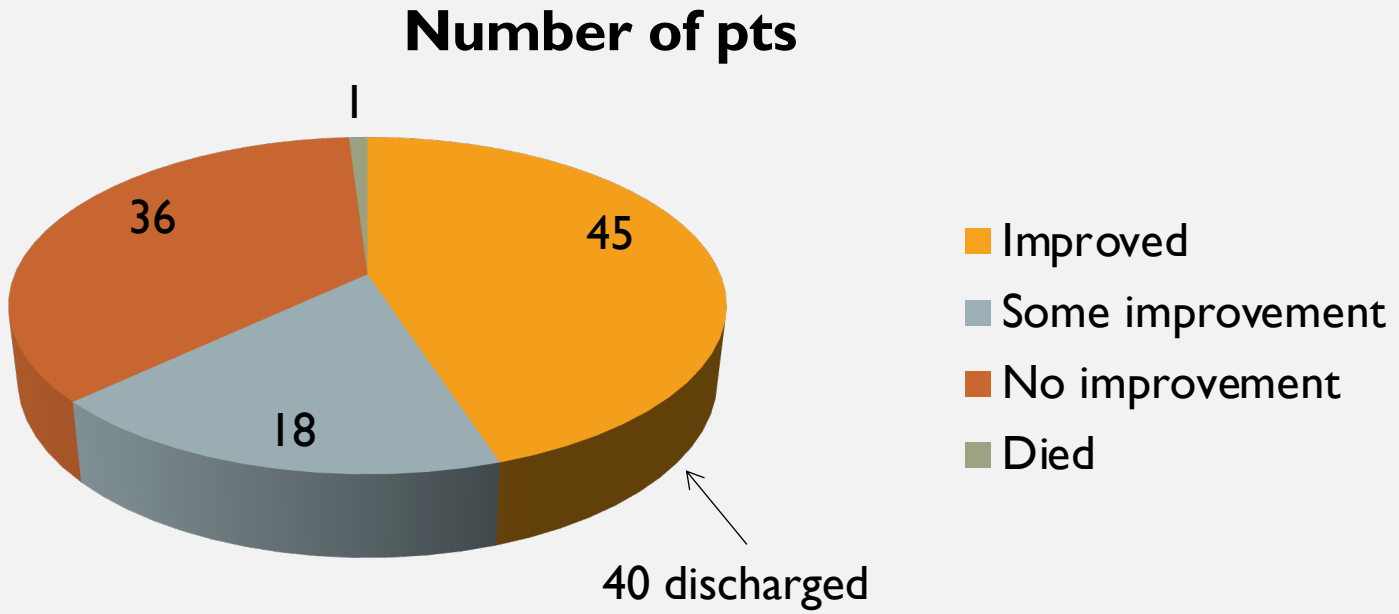
WHY DOES IT MATTER?

WHAT TO EXPECT WITH CLOZAPINE

ROUGH ESTIMATE OF OUTCOME WITH CLOZAPINE



N=100
LONG-STAY REFRACTORY PATIENTS



Wilson & Claussen 1995

WHEN TO USE CLOZAPINE?

LIEBERMAN JA, PHILLIPS M, GU H, ET AL.
ATYPICAL AND CONVENTIONAL ANTIPSYCHOTIC DRUGS IN TREATMENT-NAIVE FIRST-EPISODE SCHIZOPHRENIA: A 52-WEEK RANDOMIZED TRIAL OF CLOZAPINE VS CHLORPROMAZINE.
NEUROPSYCHOPHARMACOLOGY 2003; **28**:995-1003.

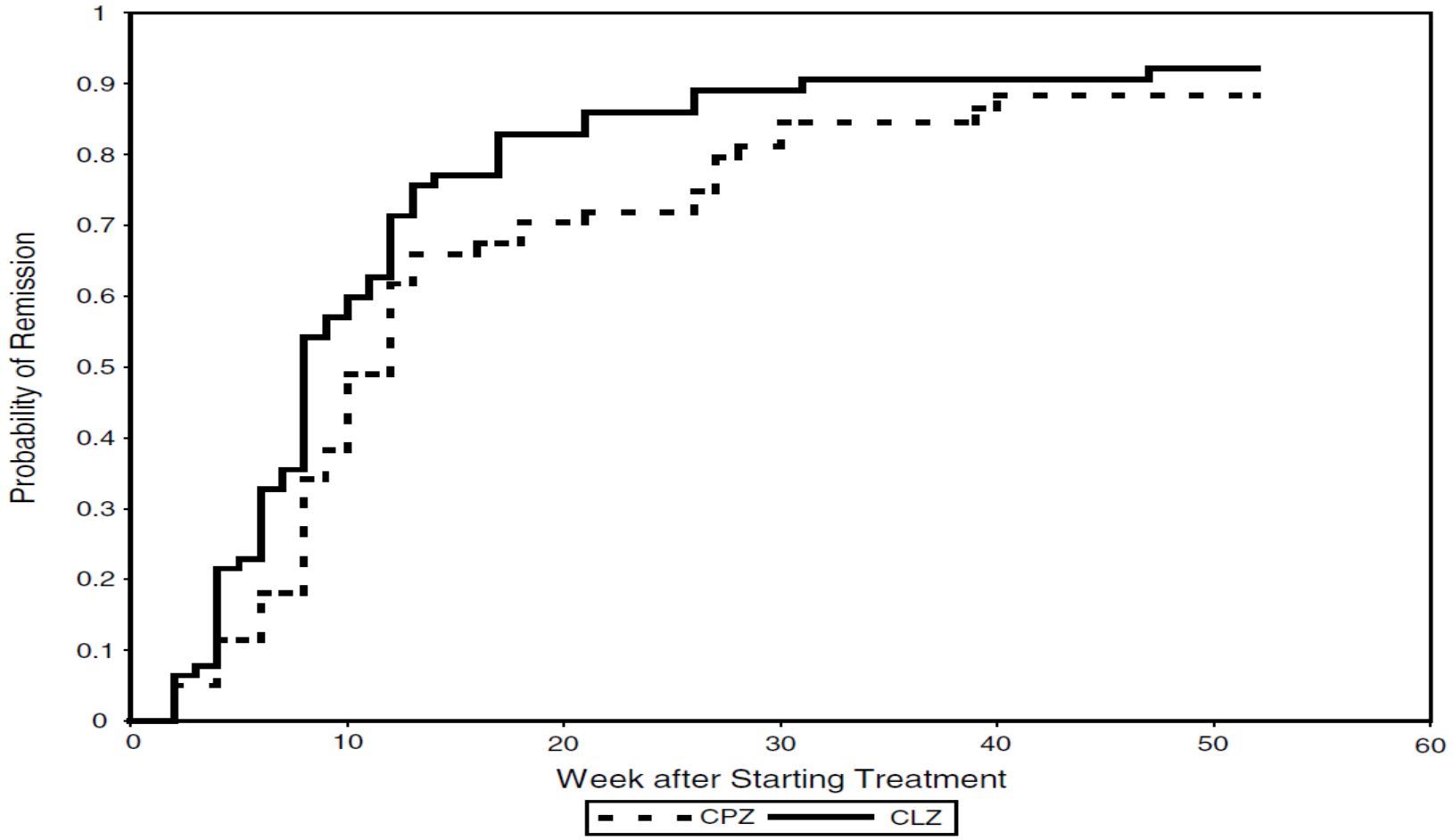
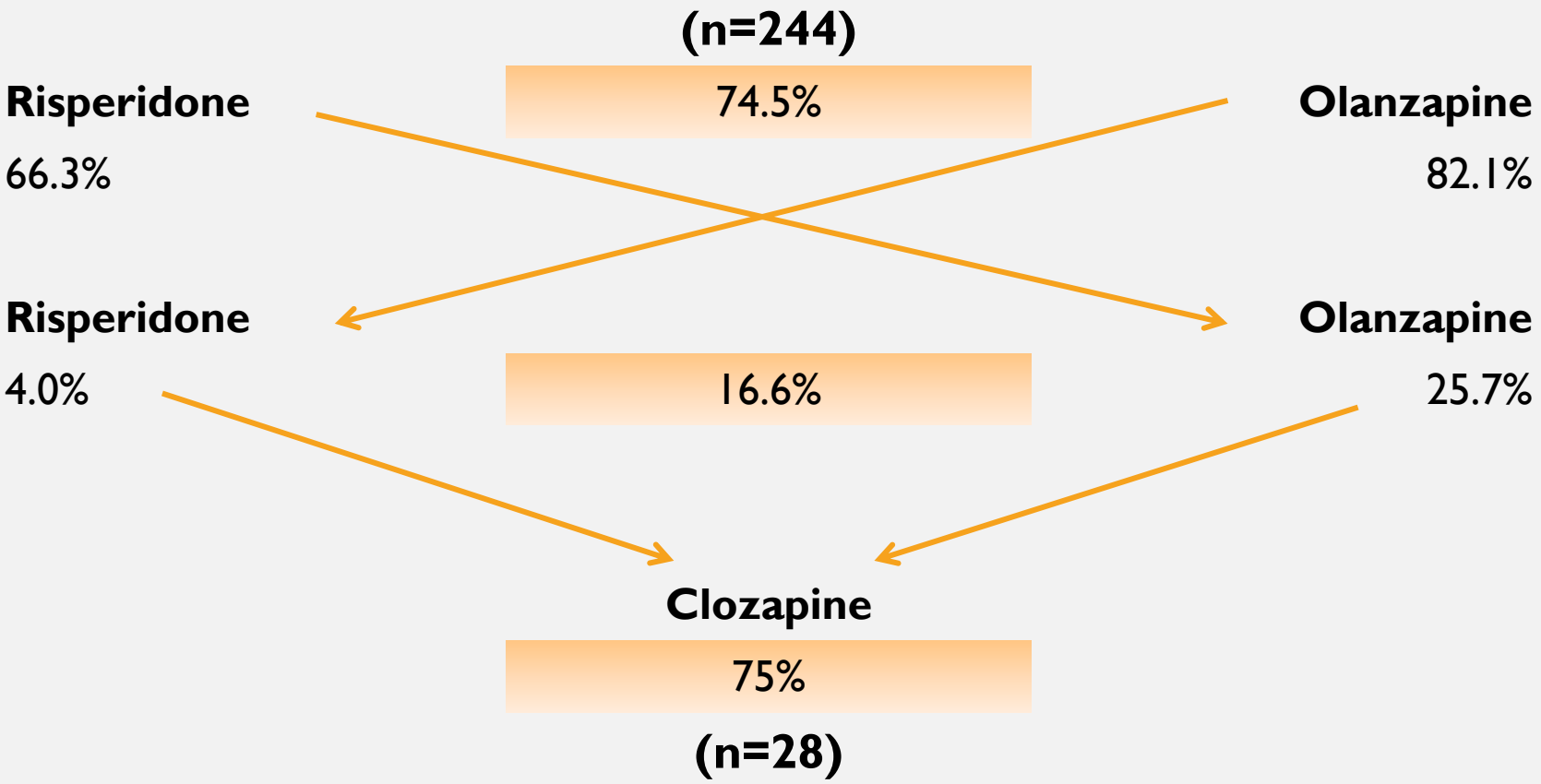


Figure 2 Kaplan–Meier remission survival plots for time to first remission for CPZ (broken line) and CLZ (solid line) groups. The median time to remission in the CLZ group was 8 and 12 weeks in the CPZ group.

AGID O ET AL, J CLIN PSYCHIATRY 2011, 72: 1439-1444

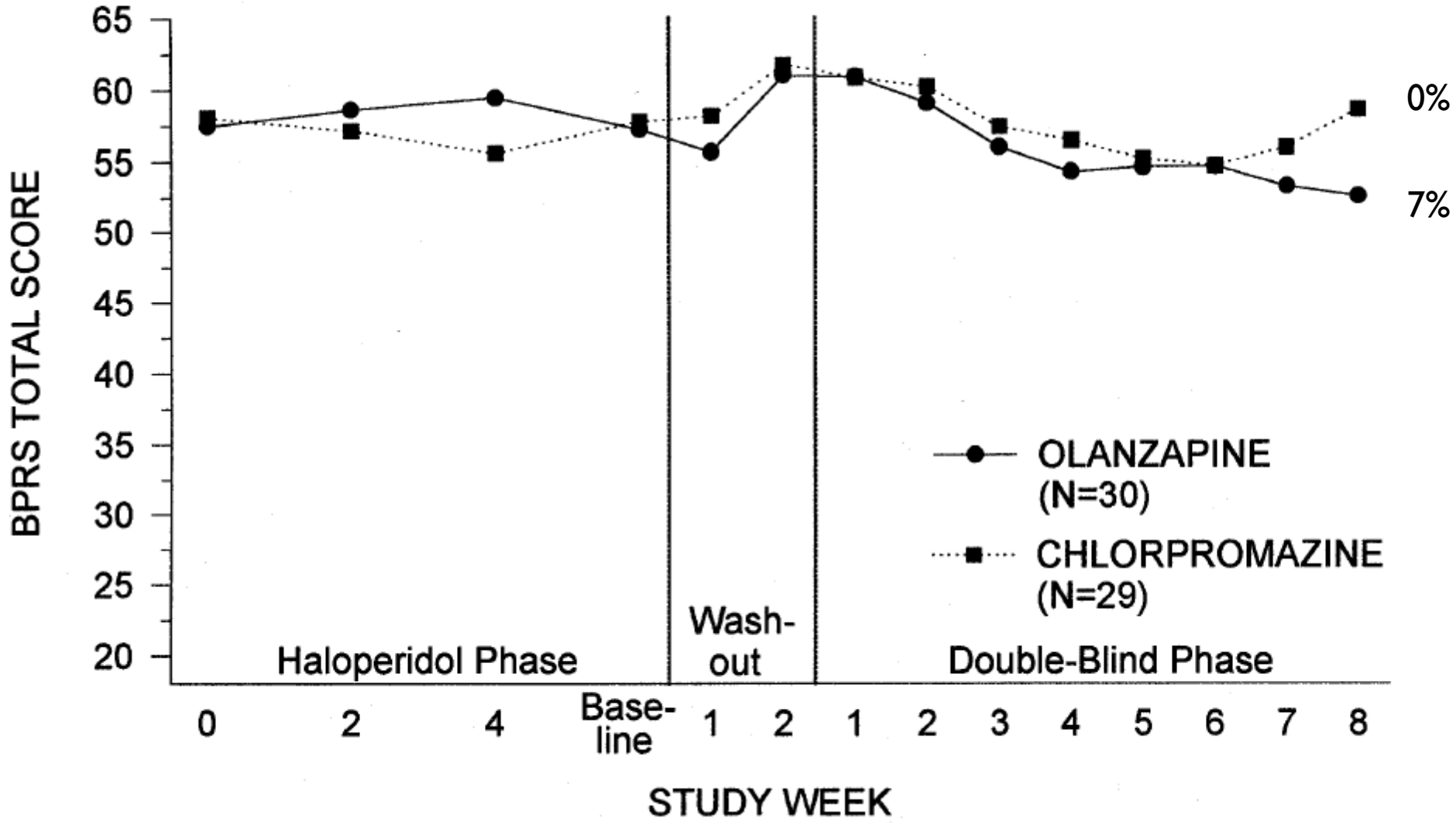


Olanzapine Compared With Chlorpromazine in Treatment-Resistant Schizophrenia

(Am J Psychiatry 1998; 155:914–920)

Robert R. Conley, M.D., Carol A. Tamminga, M.D., John J. Bartko, Ph.D., Charles Richardson, M.D., Michael Peszke, M.D., Jami Lingle, Pharm.D., Judith Hegerty, M.D., Raymond Love, Pharm.D., Cathy Gounaris, B.A., and Sandra Zaremba, R.N.

FIGURE 1. BPRS Total Scores of 59 Schizophrenic Patients Who Completed a Trial of Olanzapine or Chlorpromazine After Lack of Response to Treatment With Haloperidol



Olanzapine non-responders → Clozapine → 41% Responders

Conley RR, Schulz SC, Baker RW, Collins JF, Bell JA. Clozapine efficacy in schizophrenic nonresponders. Psychopharmacol Bull. 1988;24(2):269-74.

CHANCE OF RESPONSE IN TRS

- Clozapine 60%
- Olanzapine 7%
- Everything else 0-5%

CHANCE OF RESPONSE IN TRS

- ~~Clozapine 60%~~
- Olanzapine 7%
- Everything else 0-5%

AGRANULOCYTOSIS

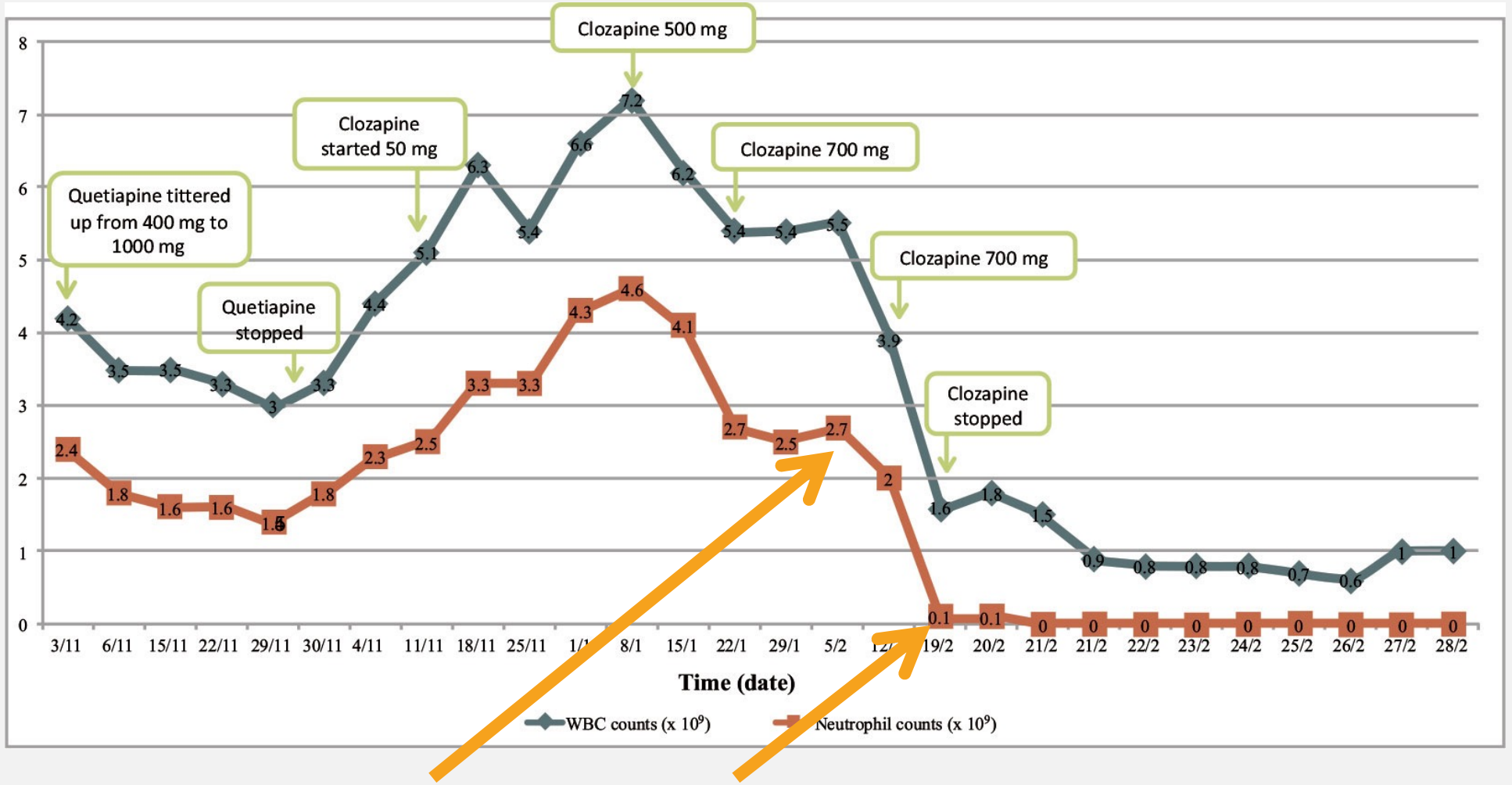
RISK OF AGRANULOCYTOSIS

(A – GRANULOCYTE – OSIS)

- Risk of agranulocytosis – 0.4% (1 in 250)
- Risk of fatal agranulocytosis – 0.05% (1 in 2000)

Li X-H et al (2020). The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. Psychological Medicine 50, 583–594.

Almaghrebi A et al Current Drug Safety Volume 14 , Issue 1 , 2019



Last count > 2.5

Neutrophil nadir 12 days later

(Time from 2.0 to 0.1 = 7 days)

BEN AND MISDIAGNOSIS OF NEUTROPENIA

Schizophrenia Bulletin
doi:10.1093/schbul/sbab006

There Is Life After the UK Clozapine Central Non-Rechallenge Database

Ebenezer Oloyede[1,2], Cecilia Casetta[2,3], Olubanke Dzahini[1,4], Aviv Segev[2,5], Fiona Gaughran[2,3], Sukhi Shergill[2,3], Alek Mijovic[6], Marinka Helthuis[7], Eromona Whiskey[1,2,3,8], James Hunter MacCabe[†,2,3,8], and David Taylor[†,1,4]

SUCCESS ON RE-EXPOSURE

- 62 pts re-exposed
- 3 recorded further ‘red’ result and were discontinued
- 59/62 (95%) successfully re-exposed and remained on clozapine
- Mean time to diagnosis of BEN – 10 years

Oloyede *et al. BMC Psychiatry* (2021) 21:502
https://doi.org/10.1186/s12888-021-03514-6

BMC Psychiatry

RESEARCH Open Access

Benign ethnic neutropenia: an analysis of prevalence, timing and identification accuracy in two large inner-city NHS hospitals

Ebenezer Oloyede[1,2*], Olubanke Dzahini[1,3], Nigel Barnes[4], Aleksandar Mijovic[5], Shreyans Gandhi[5], Sara Stuart-Smith[5], Theo de Witte[6], David Taylor[1,3†] and Eromona Whiskey[1,2,3†]

Table 3 Treatment stage of BEN diagnosis

Stage of BEN Identification	SLaM (*n* = 89) n (%)	BSMHFT[a] (*n* = 17) n (%)	Total (*n* = 106) n (%)
At Initiation	27 (30)	6 (35)	33 (32)
After Below Threshold Haematological Reaction	45 (51)	11 (65)	56 (52)
On Re-challenge	17 (19)	0 (0)	17 (16)

[a]Missing data: 5 patients

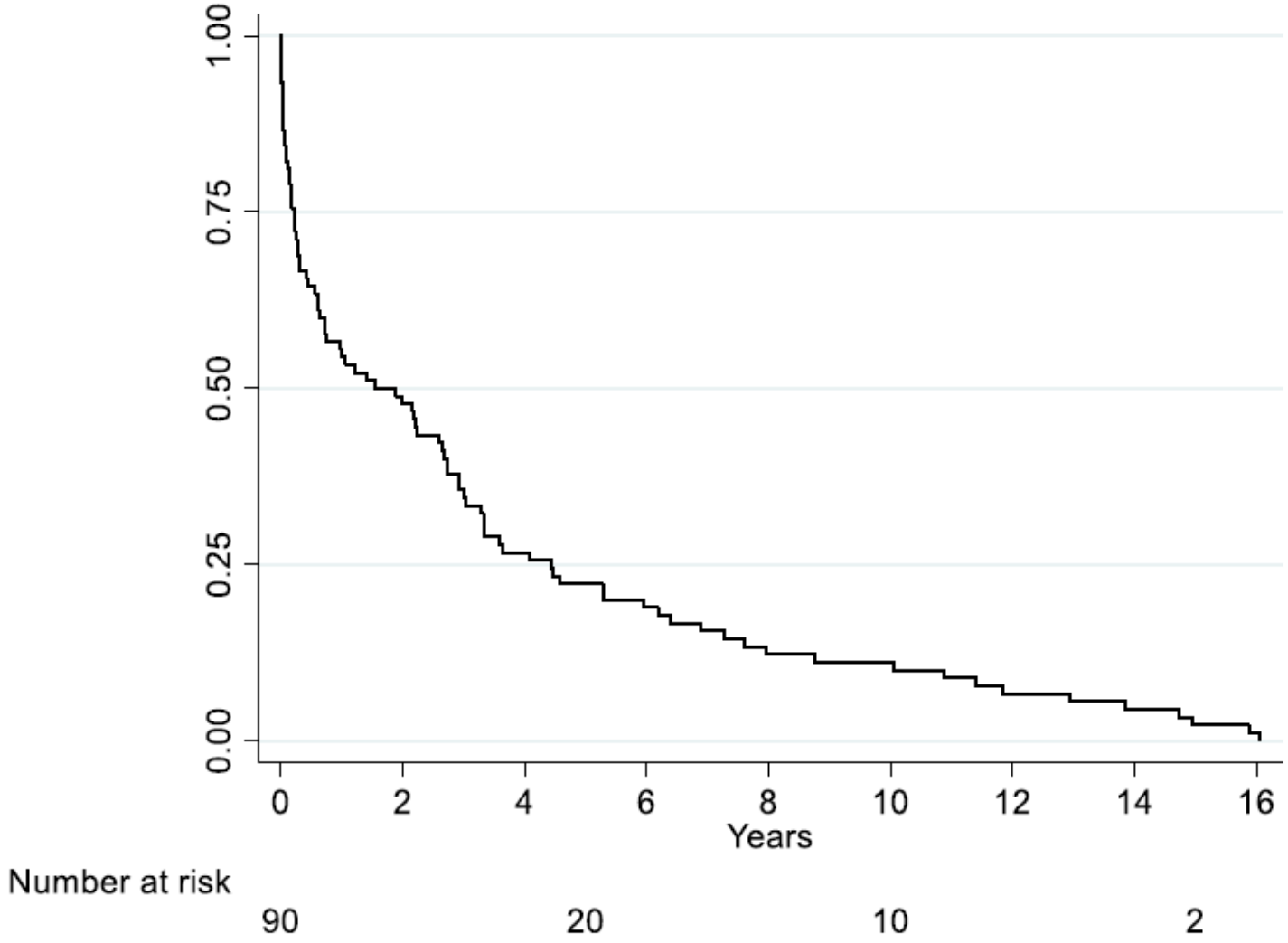


Fig. 1 Kaplan Meier for the time to BEN registration from clozapine initiation

WHAT DO WE NEED?

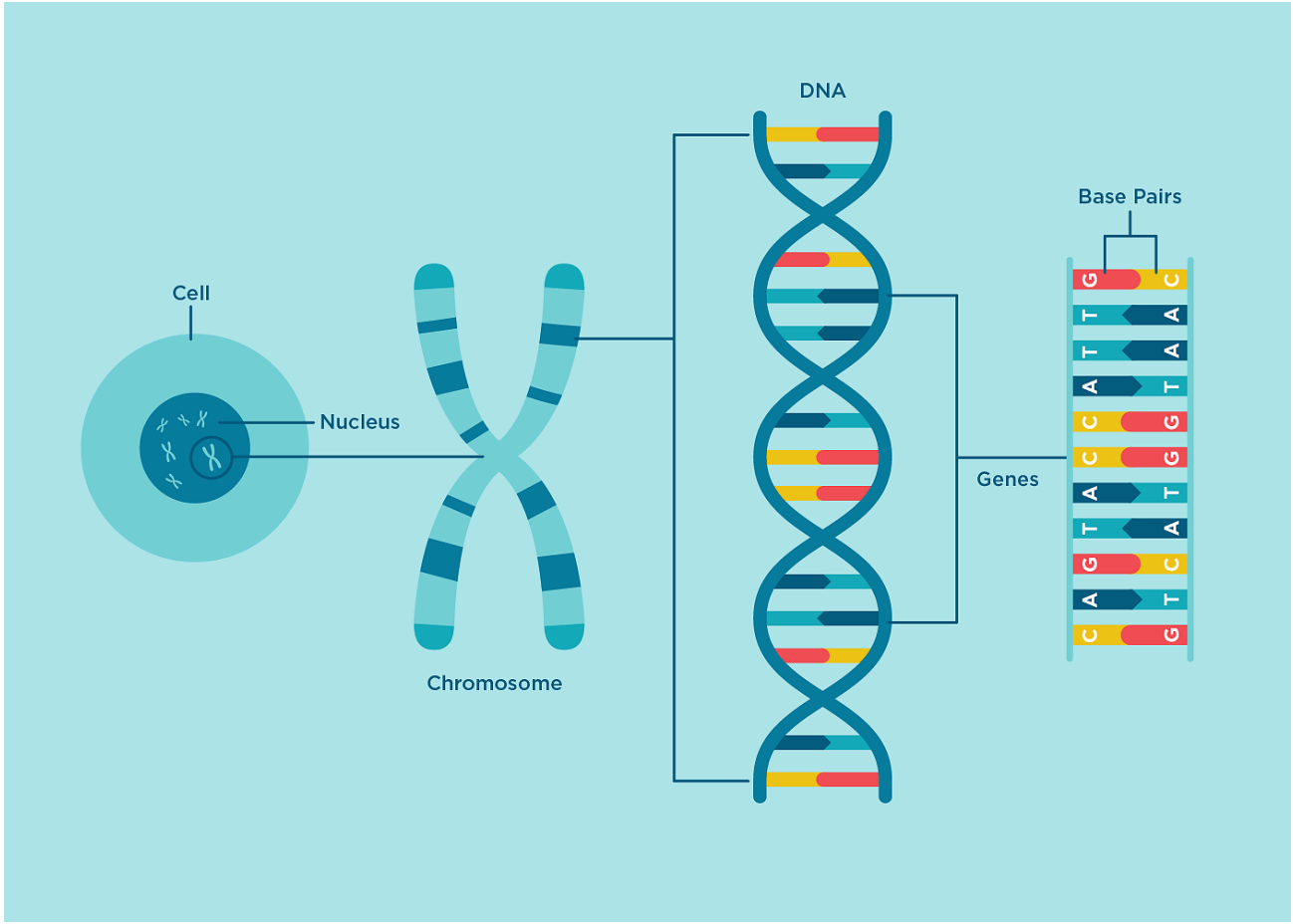
- Individual response prediction
- Individual risk of agranulocytosis
- BEN status
- Metabolic status
- Individual risk of myocarditis
- Risk of paralytic ileus

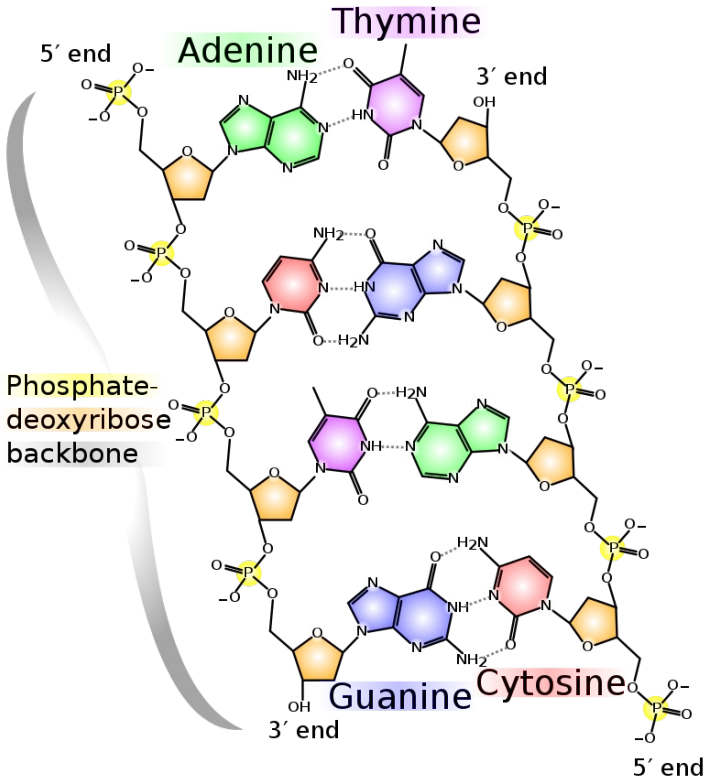
WHAT DO WE NEED?

- Individual response prediction 
- Individual risk of agranulocytosis 
- BEN status 
- Metabolic status 
- Individual risk of myocarditis 
- Risk of paralytic ileus 

Psychiatric Genetic Testing

THE PGT CLOZAPINE TEST


DNA
Base Pairs
Cell
Nucleus
Chromosome
Genes
G C
T A
T A
A T
C G
C G
A T
G C
T A
A G
C G
A T
C G


Thymine
5′ end
Adenine
3′ end
Phosphate-
deoxyribose
backbone
Guanine
Cytosine
3′ end
5′ end

RESPONSE

Three variants have been reliably shown to predict therapeutic outcome with clozapine [Gressier et al, 2016]

HTR2A rs6313C — CC carriers less likely to respond than T carriers
CC 146/272 response, CT/TT 366/596 response (54% vs 62%)

HTR2A rs6314 — C allele more likely to respond than T allele
C allele response 685/1215, T allele 55/127 (56% vs 43%)

HTR3A rs1062613 — C allele less likely to respond than T allele
C allele response 528/841, T allele 134/185 (63% vs 72%)

RESPONSE

Variant	Test result		
HTR2A_rs6313	CC	CT	TT
HTR2A_rs6314	CC	CT	TT
HTR3A_rs1062613	CC	CT	TT

27 PERMUTATIONS

Estimated chance of response (%)

95% confidence intervals (%)

Eg permutation 4

Chance of response - 20% (8-51%)

NB true value increasingly unlikely as we approach extremes of CIs

AGRANULOCYTOSIS

Four genetic variants are reliably associated with altered risk of agranulocytosis.

HLA-DQB1 Sequence variant 6672G>C (REC 21G) confers 1,175% higher risk of agranulocytosis than general population. Sensitivity 21.5%, specificity 98.4% (Athanasiou et al, 2011).
Positive predictive value 5.1%, negative predictive value 99.7%

HLA-DQB1 DQB1*0502 allele associated with agranulocytosis in 5/7 studies (eg. Dettling et al, Yunis et al). Effect size variable.

HLA-B*59:01 Presence of allele highly predictive of agranulocytosis but is rare in East Asian populations and almost absent in Caucasians. Sensitivity 31.8%, specificity 95.3% (Saito et al, 2015). PPV 6.4%, NPV 99.3%

HLA DBQ1/HLA-B Single amino acid changes HLA DBQ1 126Q and HLA-B 158 associated with increased risk of agranulocytosis. Overall 39 of 95 cases had one or both alleles; 175 of 206 controls had neither allele.

Sensitivity 41.0%, specificity 85.0% (Girardin et al, 2019; Goldstein et al 2015) (36% and 89% figures given by Legge and Walters).

The HLA-DQB1 variants and the HLA-B variants are in linkage disequilibrium [Legge et al] and are likely to convey the same association signal. Variants in LD are inherited together

AGRANULOCYTOSIS

High risk variant	6-20%
No high risk variant	0.4/0.3%

Schizophrenia

ARTICLE OPEN

Check for updates

Distinctive pattern of neutrophil count change in clozapine-associated, life-threatening agranulocytosis

David Taylor[1,2]✉, Kalliopi Vallianatou[2], Eromona Whiskey[1,2,3], Olubanke Dzahini[1,2] and James MacCabe[3,4]

The wider use of clozapine is limited by the risk of agranulocytosis and the associated requirement for monitoring of neutrophil counts. We searched local electronic patient records for cases of agranulocytosis occurring during clozapine treatment during the period 2007–2020. We found 23 episodes recorded as agranulocytosis in clozapine patients. Of these, nine met pre-defined criteria and were considered episodes of life-threatening agranulocytosis (LTA). These episodes of clozapine-induced LTA exhibited a distinct pattern of continuous and rapid neutrophil count decline to zero or near zero. Mean time for neutrophils to fall from ANC > 2 to ANC $<0.5 \times 10^9$/L was 8.4 days (range 2–15 days). Each event was also characterised by a prolonged nadir and delayed recovery (range 4–16 days). Non-LTA episodes were, in contrast, brief and benign. We conclude that an important proportion of cases of agranulocytosis identified in people prescribed clozapine are not life-threatening and may not even be clozapine-related. Monitoring schemes should aim to identify true clozapine-induced LTA as opposed to threshold-defined nominal agranulocytosis.

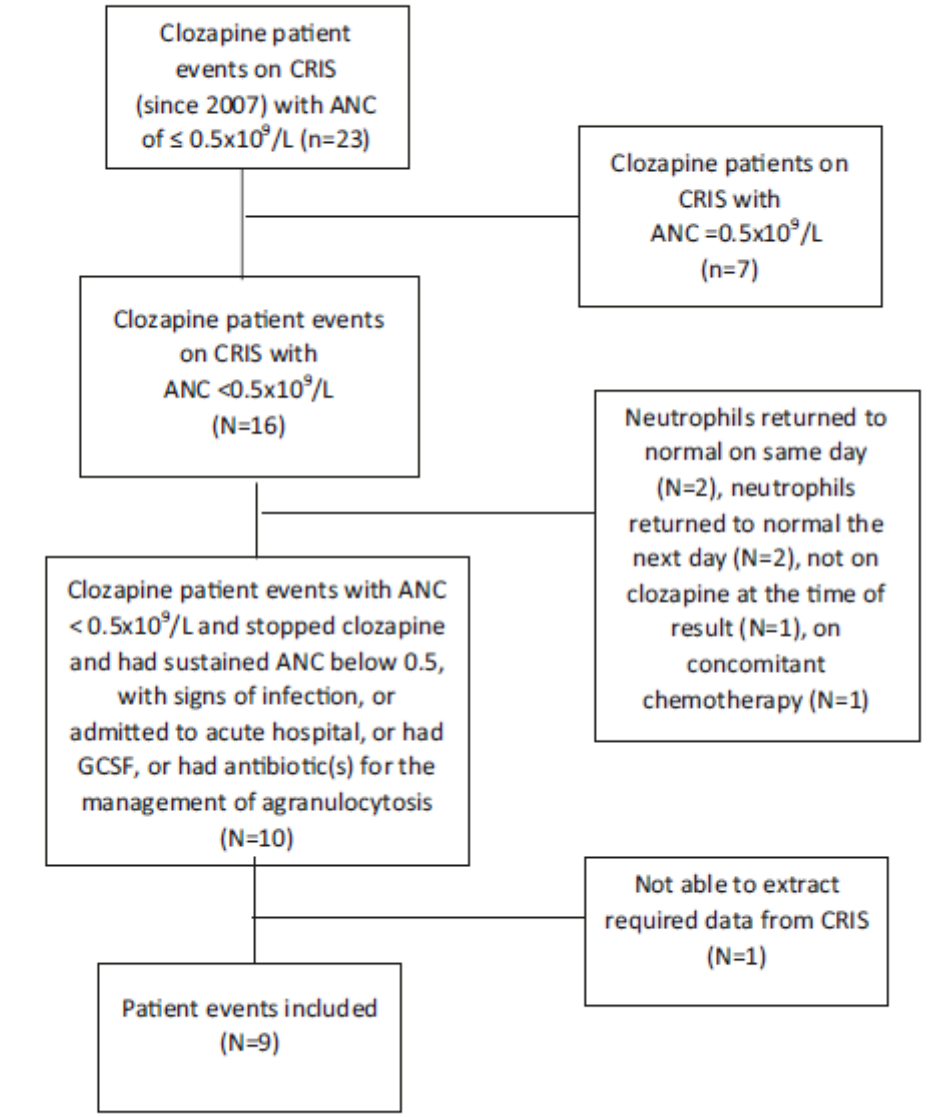
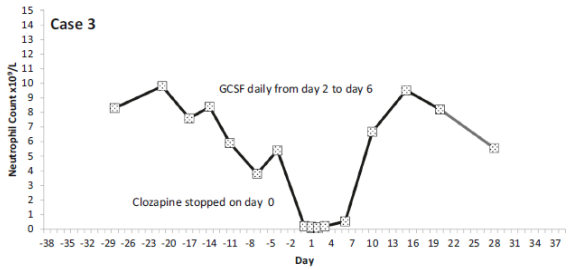
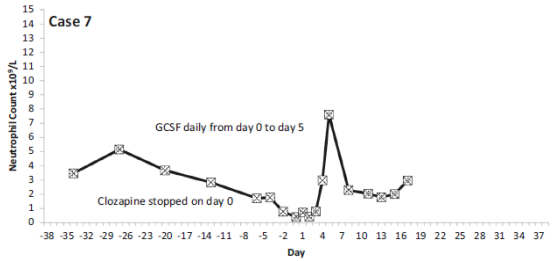
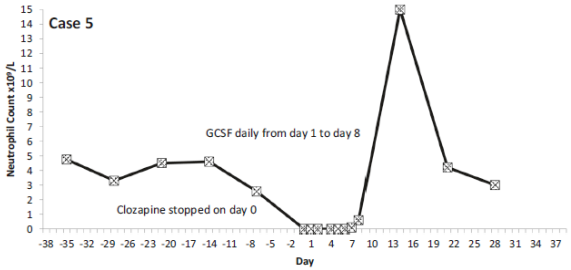


Fig. 1 Case selection.


Case 3
Neutrophil Count x10⁹/L
Day
GCSF daily from day 2 to day 6
Clozapine stopped on day 0


Case 7
Neutrophil Count x10⁹/L
Day
GCSF daily from day 0 to day 5
Clozapine stopped on day 0


Case 5
Neutrophil Count x10⁹/L
Day
GCSF daily from day 1 to day 8
Clozapine stopped on day 0

BENIGN ETHNIC NEUTROPENIA

- The absence of the red blood cell Duffy antigen, Fy (a- b-) ('Duffy Null' - SNP rs2814778 at chromosome 1q23.2) is thought to be responsible for BEN.
- "We confirmed that rs2814778 in *DARC* was associated with BEN ($p = 4.09\times10^{-53}$)." (Charles et al, 2018).
- The CC variant of this SNP codes for BEN
- As the Duffy antigen is utilized by the parasite *Plasmodium vivax* to enter the RBC, it has been hypothesized that in West Africa, positive selection for the null allele enabled individuals to be protected against infection and have a survival advantage. (Chang et al *Blood* (2018)).
- SNP rs2814778 at chromosome 1q23.2 may also be responsible for BEN in Yemenite Jews, Bedouin and those of Middle Eastern origin (Reich et al (2009)).

METABOLISM

Cytochrome p4501A2 PM/IM/EM status as normally defined by analysis of CYP1A2*1F/1C/1A/1K

Cytochrome p4503A4 PM/IM/EM status. CYP3A4 is a minor route of clozapine metabolism but metaboliser status affects blood concentration. (Toth et al, 2017)

Cytochrome p4503A5 PM/IM/EM status. CYP3A5 PM status associated with elevated clozapine blood levels (John et al, 2020)

Other non-CYP genetic associations have also been demonstrated.

NFIB rs28379954 ***T>C*** CT carriers have much lower blood concentrations than TT carriers in both smokers and non-smokers (Smith et al, 2020)

Also the **rs2472297** (?CYP1A1) genotype independently predicts clozapine plasm levels. (Pardinas et al, 2019). Levels are highest in C/C carriers and lowest in T/T carriers (C/T somewhere in between).

The Clozapine Test report

healthincode

Psychiatric Genetic Testing

PATIENT INFORMATION	SAMPLE		REFERRING PHYSICIAN
ID	Sample number		Name
Sex	Source		Institution
DOB	Date received		
Ref.	Date of report	21 Jan 2021	
EHR ID			

Test results for: SAMPLE REPORT

Reason for the study: Non-response to clozapine, smoking status - daily but more than 20 cigarettes a day
Test(s) requested: Clozapine pharmacogenetics test [10 genes]

PHARMACOGENETIC STUDY: CLOZAPINE PHARMACOGENETICS TEST [10 GENES]

Likelihood of response: **BELOW AVERAGE (20%)**
This is the calculated best estimate of the chances of response for this patient. The credible range of values for this patient is **8-51%.** The likelihood of response in the general population is **60%.**

Risk of agranulocytosis: **AVERAGE (0.4%).**
Follow standard full blood count monitoring: weekly for 18 weeks, then fortnightly up to 1 year, then monthly (schedule varies from country to country)

Benign ethnic neutropenia status: **NEGATIVE**
Absolute neutrophil count (ANC) standard limits apply. Normal range for the general population.

Rate of clozapine metabolism: **HIGH**

Recommended starting dose: **12.5mg** and rapid titration, according to tolerability

Recommended target dose: **575mg a day** in divided doses

Risk and response categories classification was developed with an algorithm considering independence within and between the genetic and environmental risk factors included.

PHARMACOGENETIC STUDY: CLOZAPINE PHARMACOGENETICS TEST [10 GENES]

Likelihood of response: **BELOW AVERAGE (20%)**

This is the calculated best estimate of the chances of response for this patient. The credible range of values for this patient is **8-51%.** The likelihood of response in the general population is **60%.**

Risk of agranulocytosis: **AVERAGE (0.4%).**

Consider a standard full blood count monitoring; weekly for 18 weeks, then fortnightly up to 1 year, then monthly (schedule varies from country to country)

Benign ethnic neutropenia status: **NEGATIVE**

ANC standard limits apply. Normal range for the general population (ANC greater than or equal to 1500/µL).

Rate of clozapine metabolism: **HIGH**

Recommended starting dose: **12.5 mg and rapid titration**

Recommended target dose: **575 mg a day in divided doses**

Risk and response categories classification was developed with an algorithm considering independence within and between the genetic and environmental risk factors included.

ONE-OFF TEST

• Likelihood of response	(% + CI)
• High risk variant for agranulocytosis	Yes/No
• BEN	Yes/No
• Target dose	To nearest 25mg

Psychiatric Genetic Testing

PGT TEST

Where to start?

PRIORITY 1

- All current clozapine patients (regardless of apparent ethnicity) with unknown BEN status
- All prospective clozapine patients
- All current clozapine patients who cannot achieve therapeutic plasma levels

PRIORITY 2

- All current clozapine patients who have not responded to clozapine
- All current clozapine patients starting or stopping an interacting drug
- All current clozapine patients with suspected agranulocytosis/red result
- All current clozapine patients who have high or very high therapeutic plasma levels

THANK YOU