30 YEARS OF CLOZAPINE

CLOZAPINE

Where I come in

1958	1971	1975	1990	2023
Synthesised	First RCT	Withdrawn	Reintroduced	

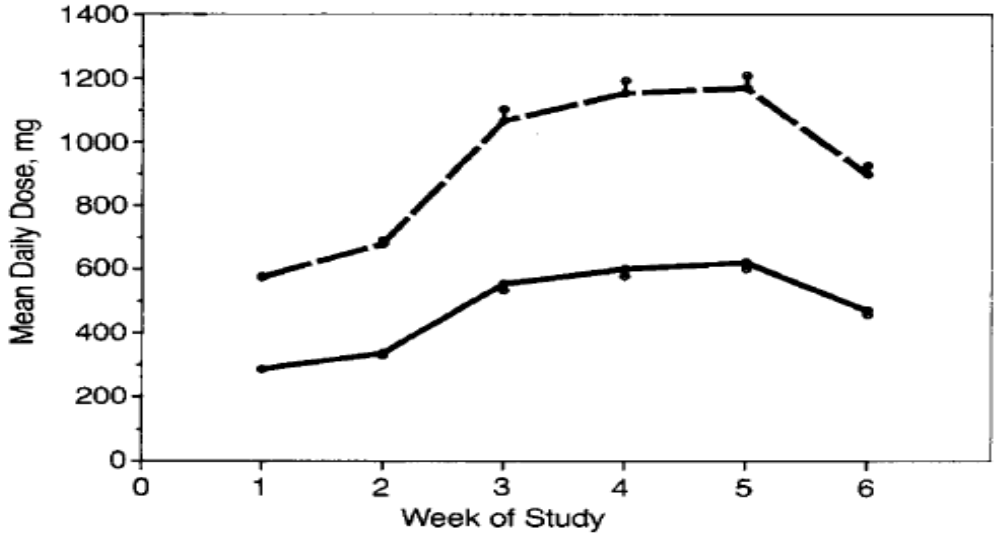


Fig 1.—Mean daily doses of clozapine (solid line) and chlorpromazine (broken line) during double-blind phase of study (period 4). For clozapine, at week 1, n = 126; week 2, n = 126; week 3, n = 122; week 4, n = 120; week 5, n = 119; and week 6, n = 116. For chlorpromazine, at week 1, n = 141; week 2,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

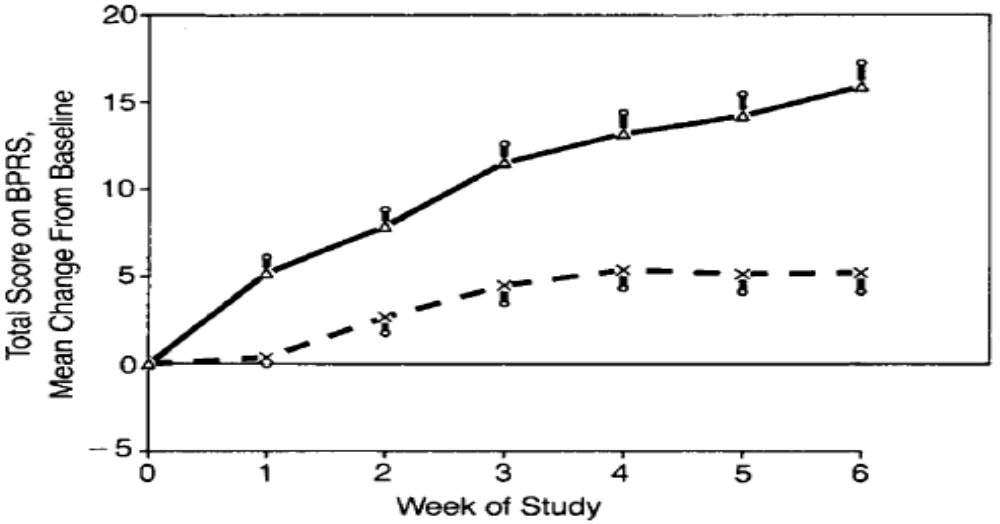


Fig 2.—Mean change from baseline in total score on Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztropine mesylate (broken line, n = 139). $P<.001$ during each week of study.

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

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.

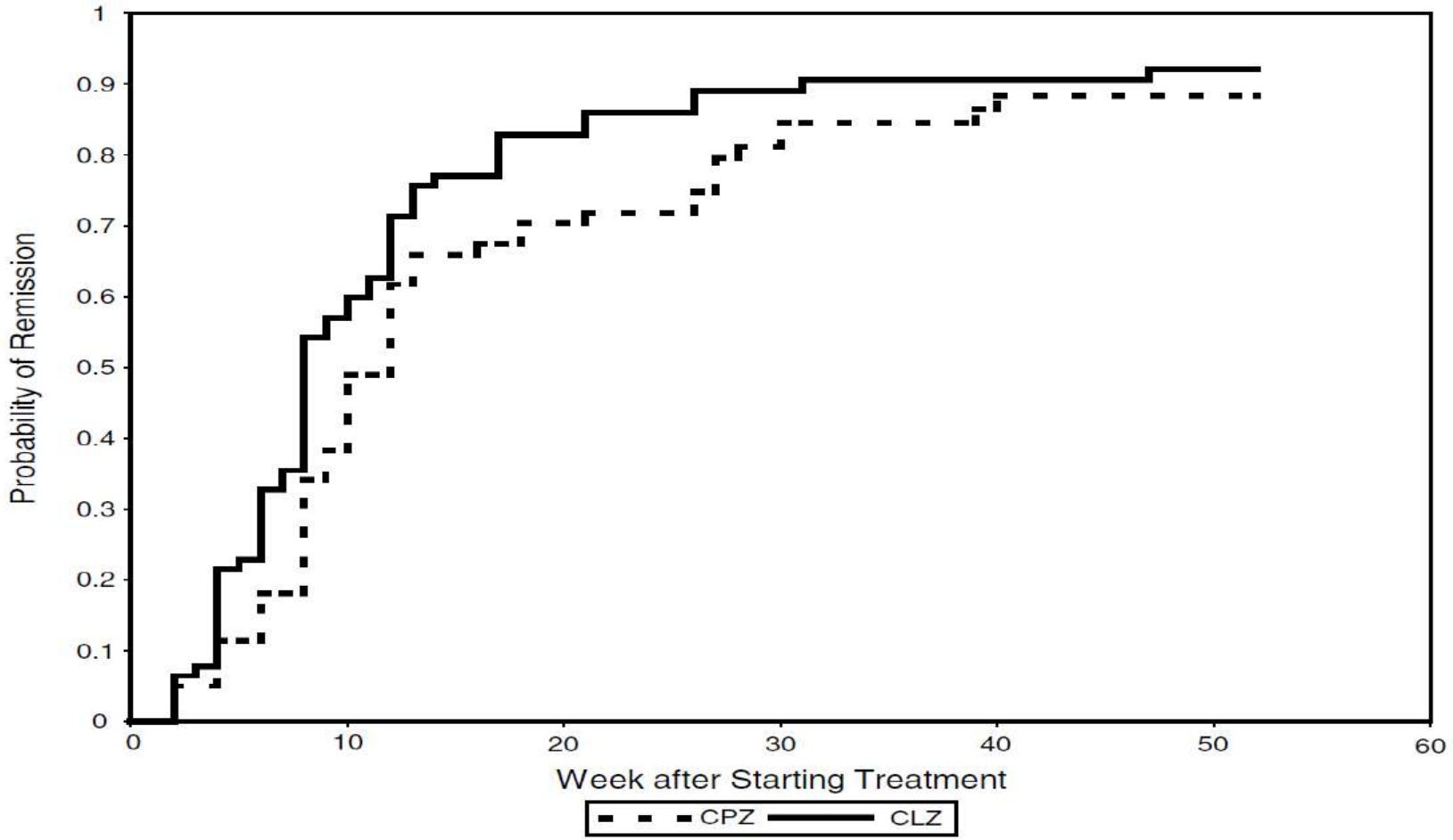
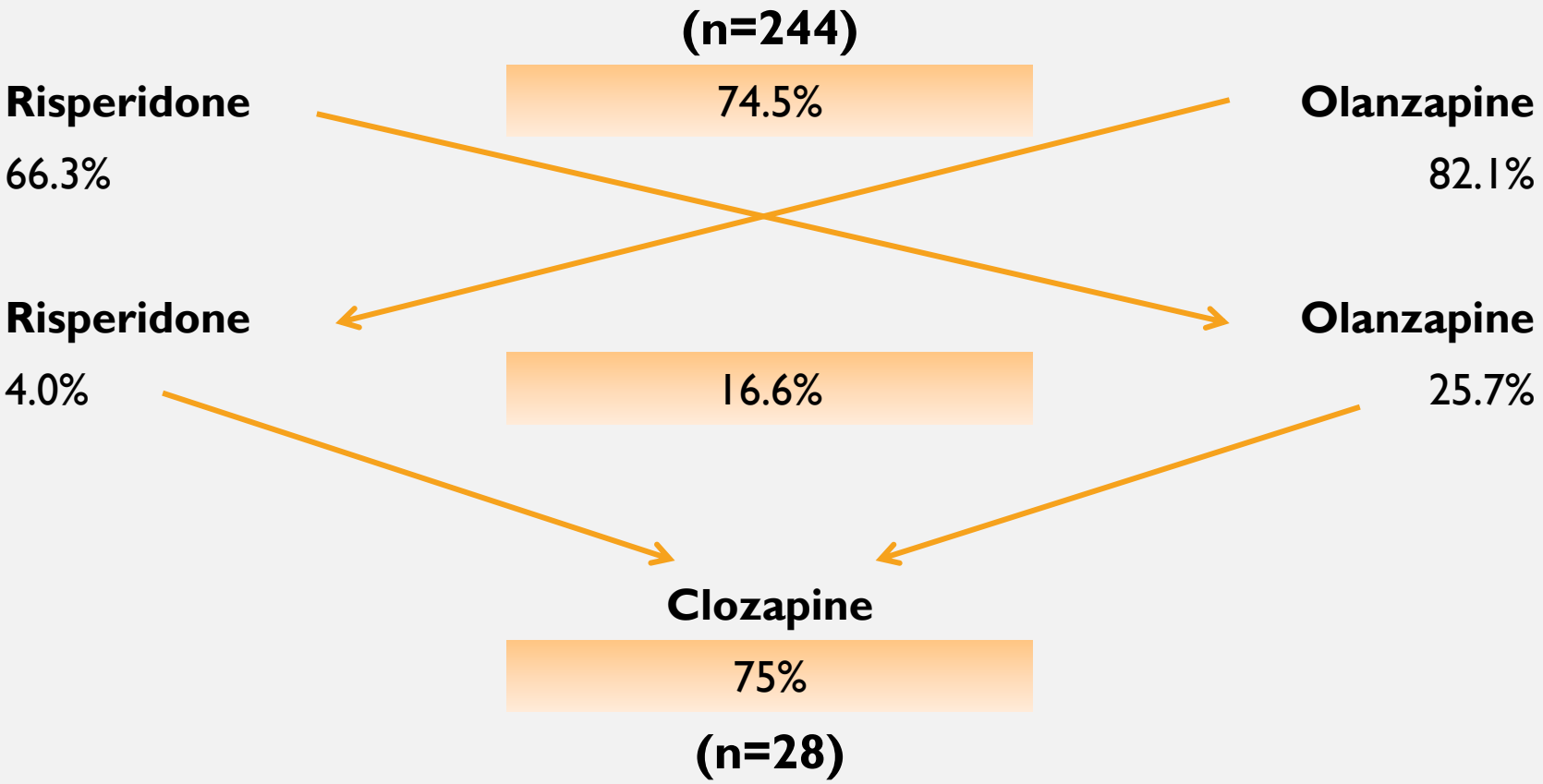


Figure 2 Kaplan–Meier remission survival plots for time to first remission for CPZ (broken line) and CLZ (solid line) groups. The median time to remission in the CLZ group was 8 and 12 weeks in the CPZ group.

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

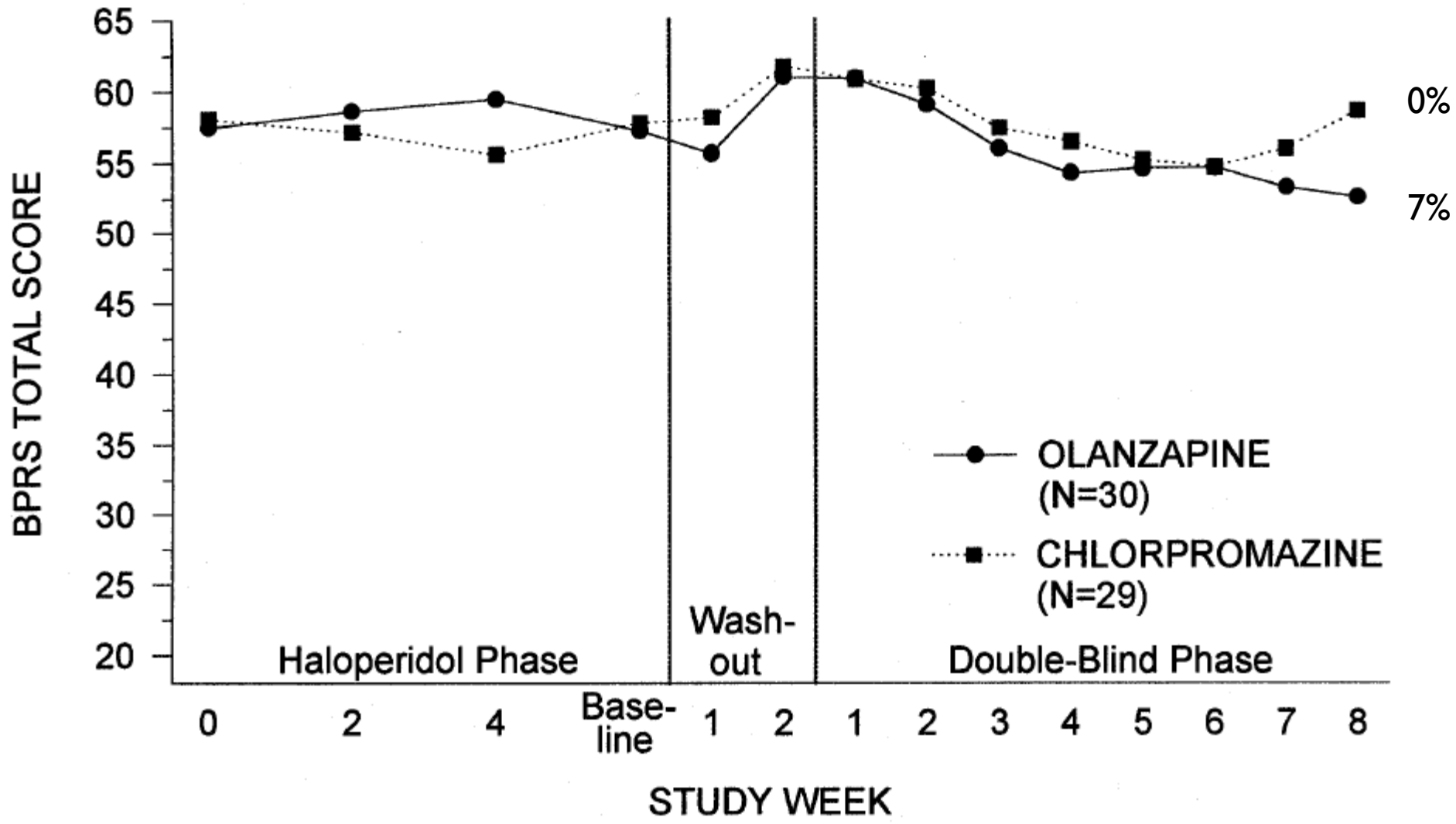


Olanzapine Compared With Chlorpromazine in Treatment-Resistant Schizophrenia

[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%

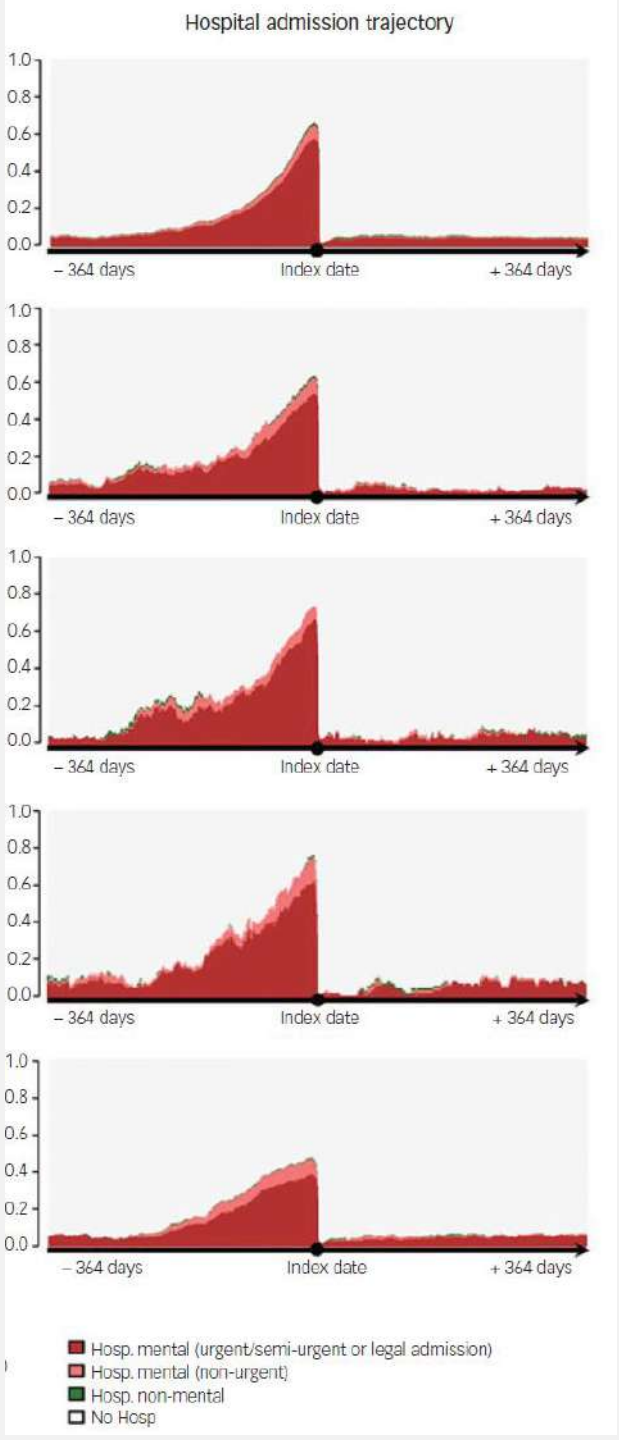
JUST FYI…..

BJPsych The British Journal of Psychiatry (2022)
220, 347–354. doi: 10.1192/bjp.2022.1

Association between previous and future antipsychotic adherence in patients initiating clozapine: real-world observational study

Sébastien Brodeur*, Josiane Courteau*, Alain Vanasse, Mireille Courteau, Emmanuel Stip, Marie-Josée Fleury, Alain Lesage, Marie-France Demers, Olivier Corbeil, Laurent Béchard and Marc-André Roy

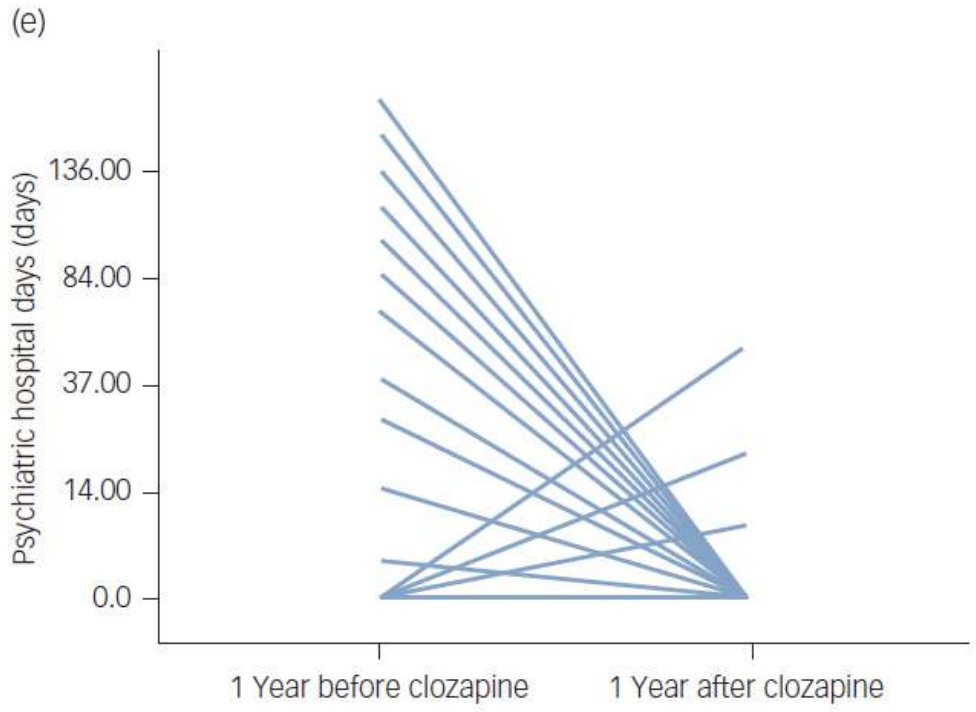
Hospital admission before and after clozapine initiation

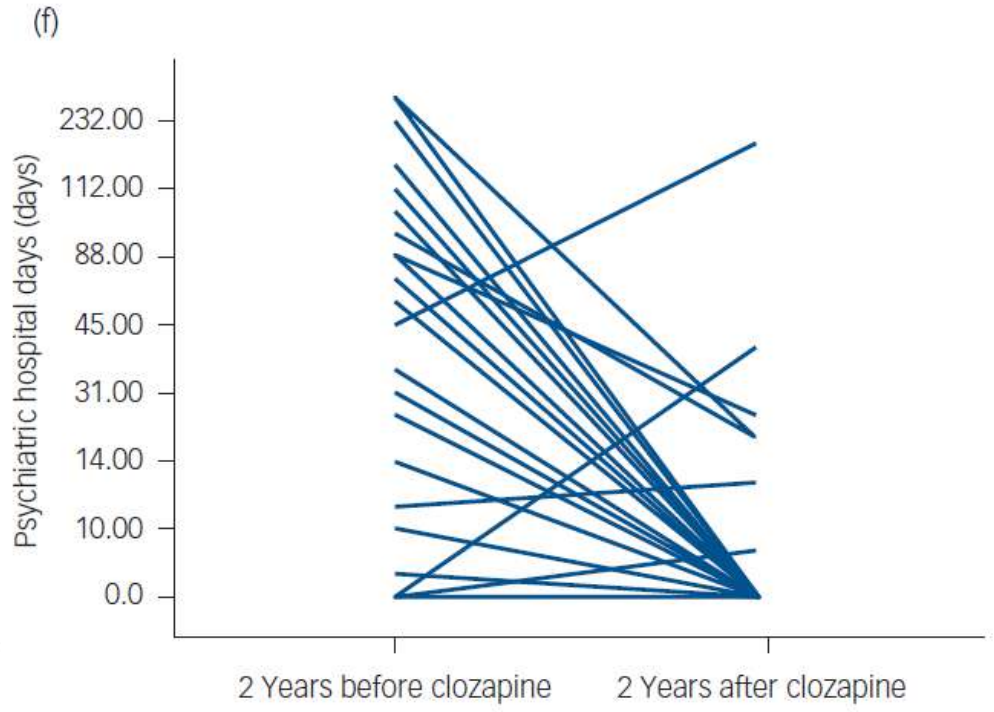


BJPsych
The British Journal of Psychiatry (2022)
Page 1 of 8. doi: 10.1192/bjp.2022.47

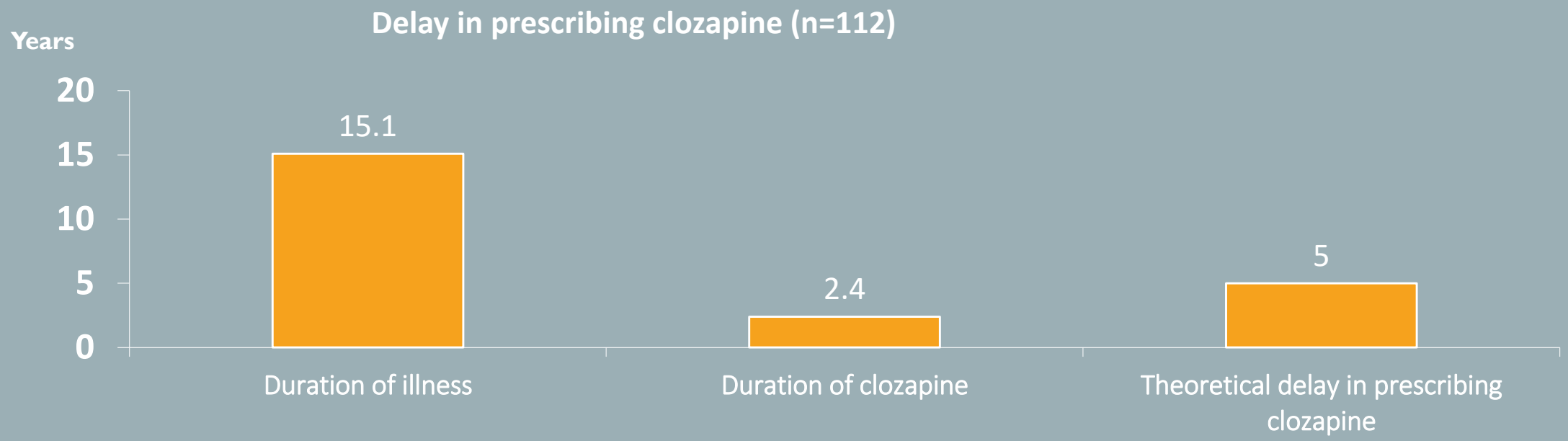
Real-world clinical and cost-effectiveness of community clozapine initiation: mirror cohort study

Emma Butler, Toby Pillinger, Kirsten Brown, Faith Borgan, Alice Bowen, Katherine Beck, Enrico D'Ambrosio, Lisa Donaldson, Sameer Jauhar, Stephen Kaar, Tiago Reis Marques, Robert A. McCutcheon, Maria Rogdaki, Fiona Gaughran, James MacCabe, Rosalind Ramsay, David Taylor, Paul McCrone, Alice Egerton and Oliver D. Howes


(e)
Psychiatric hospital days (days)
136.00
84.00
37.00
14.00
0.0
1 Year before clozapine
1 Year after clozapine


(f)
Psychiatric hospital days (days)
232.00
112.00
88.00
45.00
31.00
14.00
10.00
0.0
2 Years before clozapine
2 Years after clozapine

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

THERAPEUTIC ADVANCES in
Psychopharmacology

Original Research

Clozapine for treatment resistance in early psychosis: a survey of UK clinicians' training, knowledge and confidence

Ebenezer Oloyede*, Bethany Mantell*, Julie Williams, Serena Lai, Sameer Jauhar, David Taylor, James H. MacCabe, Robert Harland, Philip McGuire† and Graham Blackman†

Ther Adv Psychopharmacol

2022, Vol. 12: 1–7

DOI: 10.1177/20451253221141222

Abstract

Background: Clozapine is the only medication licenced for patients with psychosis that is resistant to conventional antipsychotic treatment. However, despite its effectiveness, it remains widely underutilised. One contributory factor for this may be clinicians' lack of confidence around the management of clozapine.

Objective: We conducted a survey of clinicians working in Early Intervention in Psychosis (EIP) services to determine their training needs for clozapine management in EIP services.

Methods: An electronic survey was made available to all clinicians working in EIP services in England. The survey assessed confidence and training needs regarding managing clozapine in patients with treatment-resistant psychosis. Quantitative data were analysed using total mean scores and the Mann–Whitney *U* test.

Results: In all, 192 (27%) of approximately 700 clinicians from 35 EIP services completed the survey. Approximately half (54%) had not received training on treatment with clozapine. Experience of training was higher in prescribers than non-prescribers, and among medical than non-medical clinicians. Previous training was associated with significantly higher confidence in offering clozapine and managing treatment-resistant psychosis ($p < 0.001$). Confidence levels with managing treatment-resistant psychosis and clozapine were relatively high (mean = 4 out of 5, SD = 1). Respondents were most confident about monitoring mental health response to treatment (mean = 5, SD = 1). Participants were least confident about how to discontinue clozapine treatment safely (mean = 3, SD = 1).

Conclusion: Most clinicians working in EIP have not received training on the use of clozapine. This may account, in part, for the underutilisation of clozapine in EIP services. The provision of training in the identification of treatment-resistant psychosis and the use of clozapine will likely improve the detection and management of treatment resistance in the early phase of psychosis.

Keywords: clozapine, early intervention, treatment-resistant psychosis, training

Received: 23 August 2022; revised manuscript accepted: 1 November 2022.

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Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

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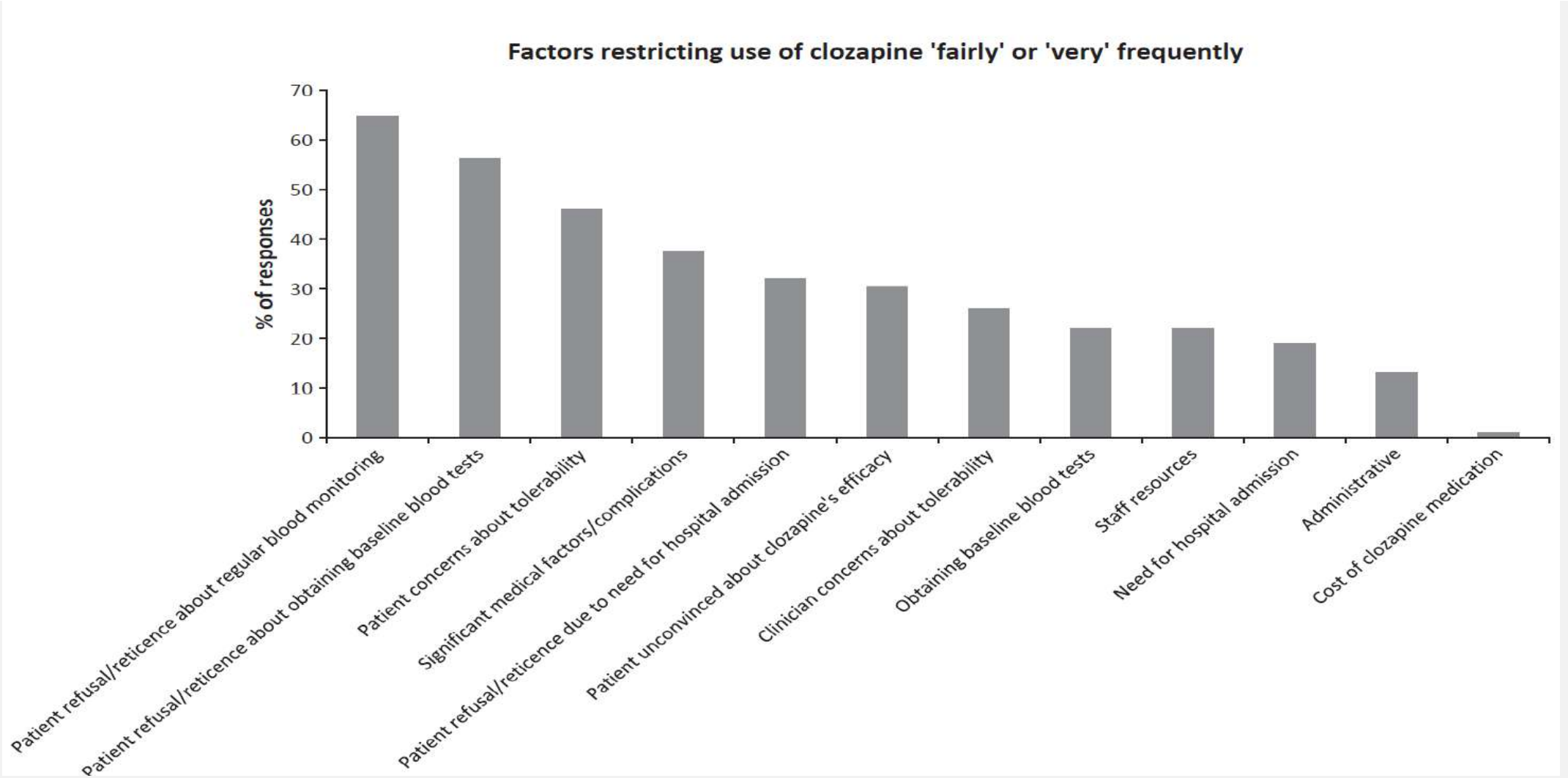
Acta Psychiatr Scand 2014: 130: 16–24

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



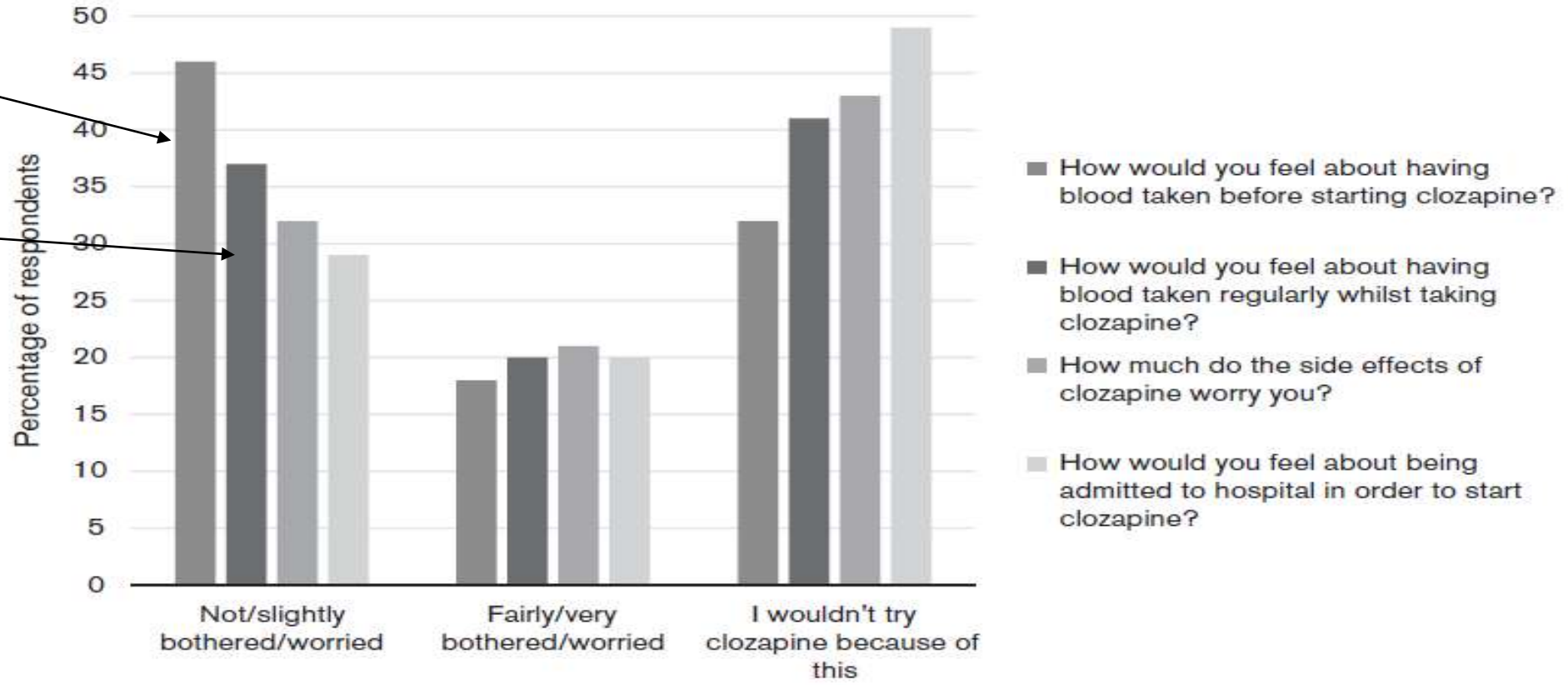
International Clinical Psychopharmacology 2017, 32:337–342

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%

VARIATION IN THE USE OF CLOZAPINE

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. Garuoliene[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 Clinic, 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

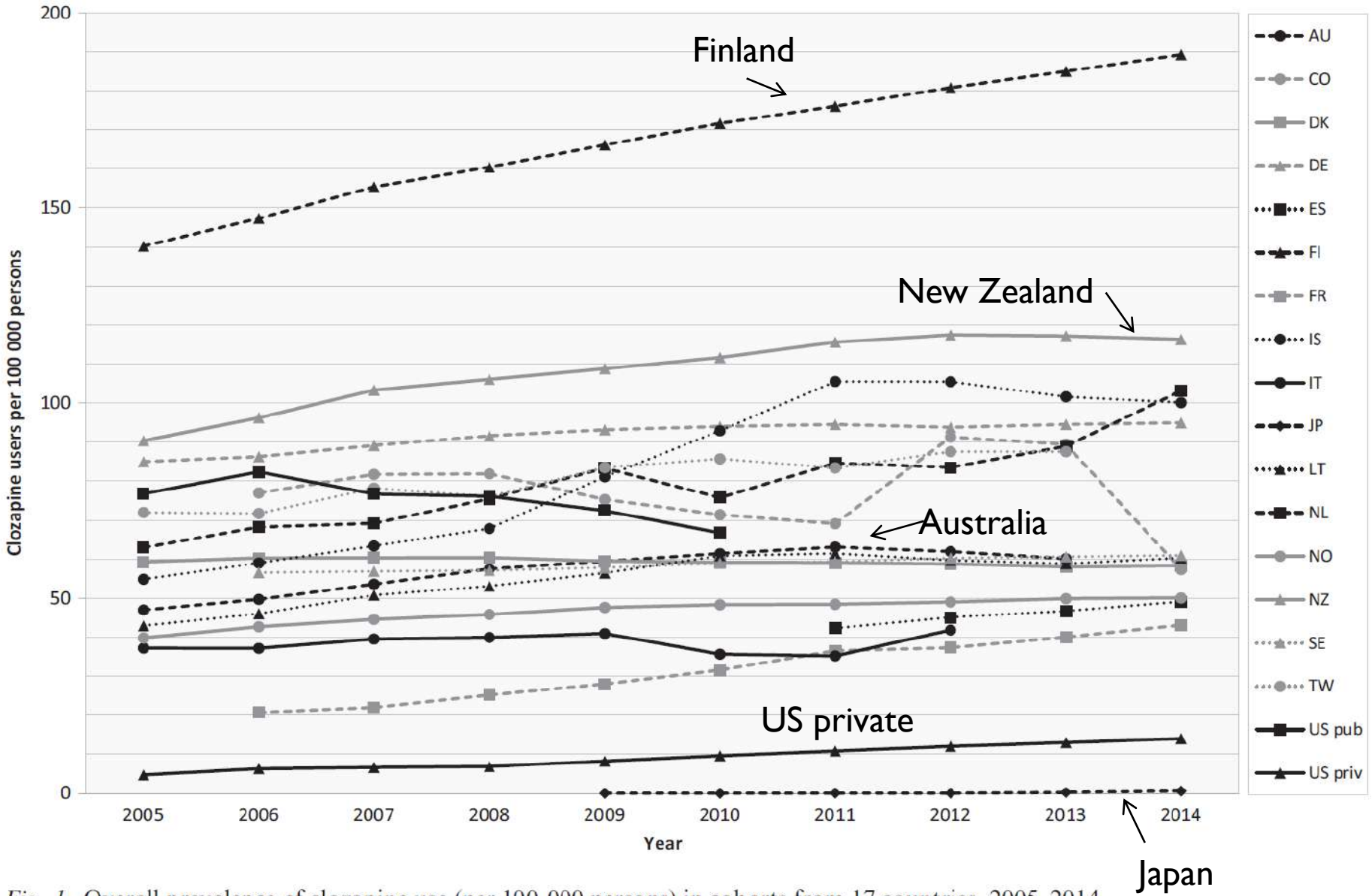


Fig. 1. Overall prevalence of clozapine use (per 100 000 persons) in cohorts from 17 countries, 2005–2014.

DOI: 10.1111/acps.13280

ORIGINAL ARTICLE

Acta Psychiatrica Scandinavica WILEY

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%

Clozapine haematological monitoring for neutropenia: a global perspective

Ebenezer Oloyede[1,2], Graham Blackman[2], Eromona Whiskey[1,3,4], Christian Bachmann[5,6], Olubanke Dzahini[1,4], Sukhi Shergill[2], David Taylor[1,3], Philip McGuire[2,*] and James MacCabe[2,4,7,*]

Epidemiology and Psychiatric Sciences

cambridge.org/eps

Original Article

*Joint Senior authors.

Cite this article: Oloyede E, Blackman G, Whiskey E, Bachmann C, Dzahini O, Shergill S, Taylor D, McGuire P, MacCabe J (2022). Clozapine haematological monitoring for neutropenia: a global perspective. *Epidemiology and Psychiatric Sciences* **31**, e83, 1–10. https://doi.org/10.1017/S204579602200066X

Received: 19 July 2022
Revised: 26 October 2022
Accepted: 27 October 2022

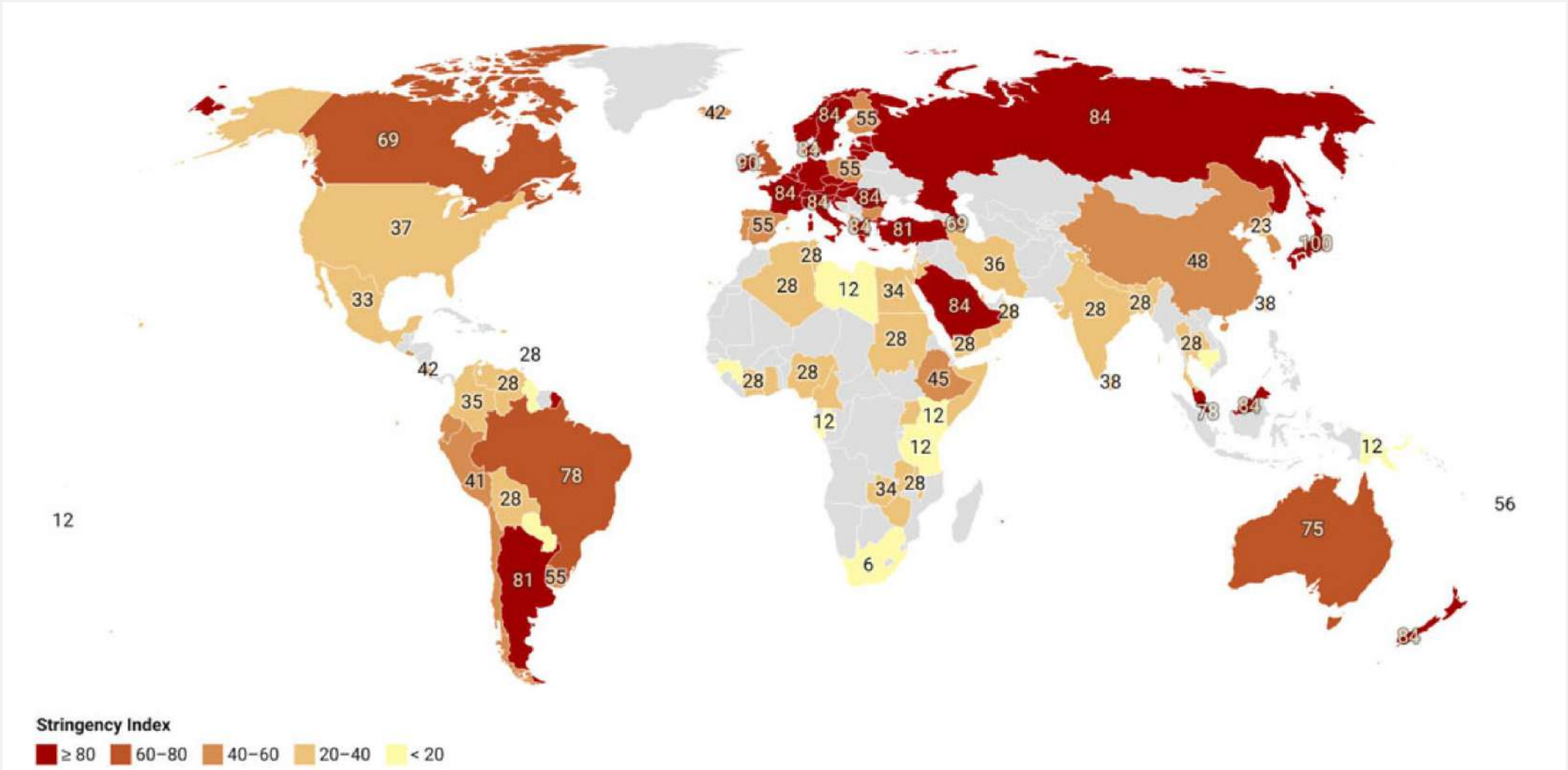
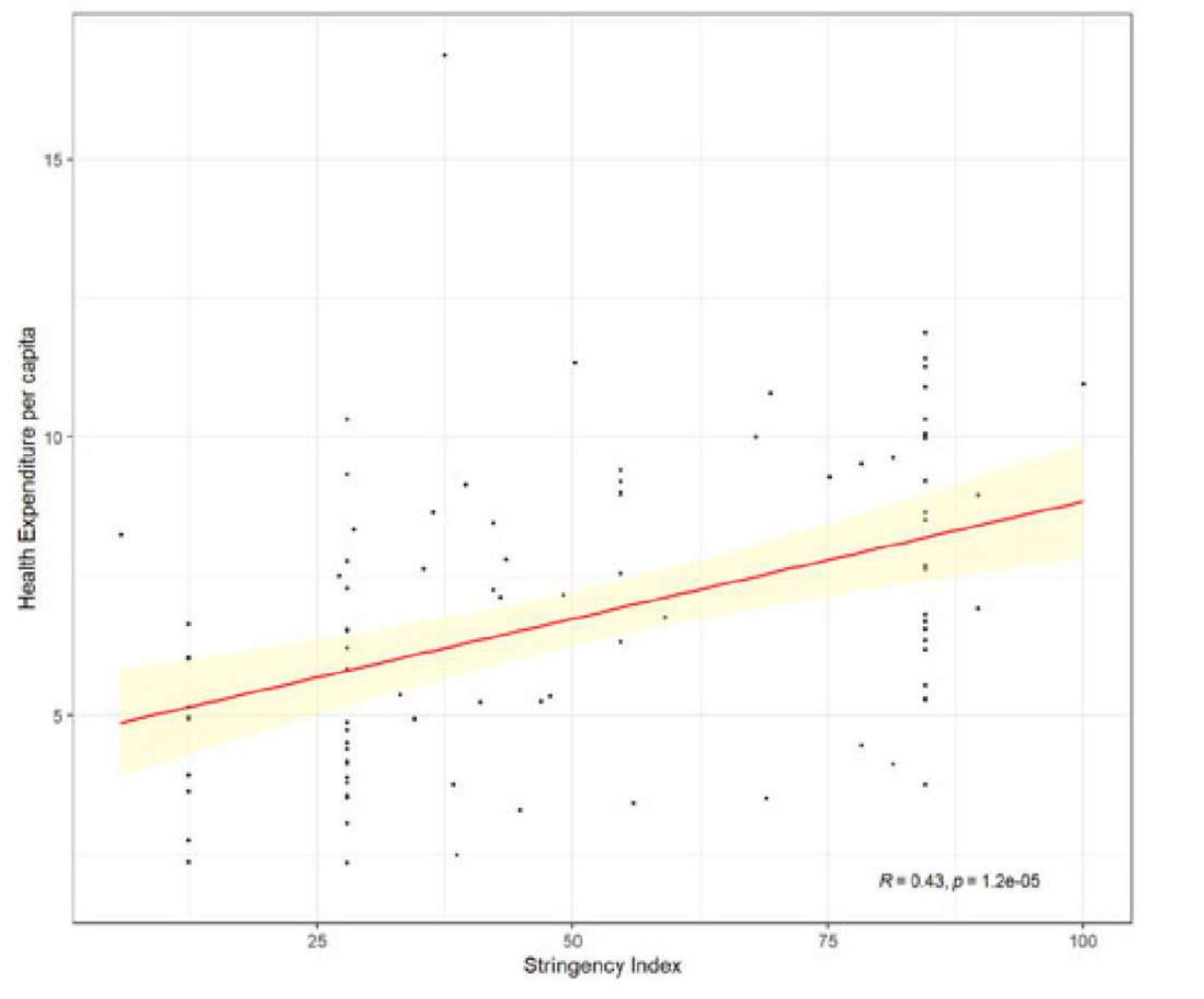
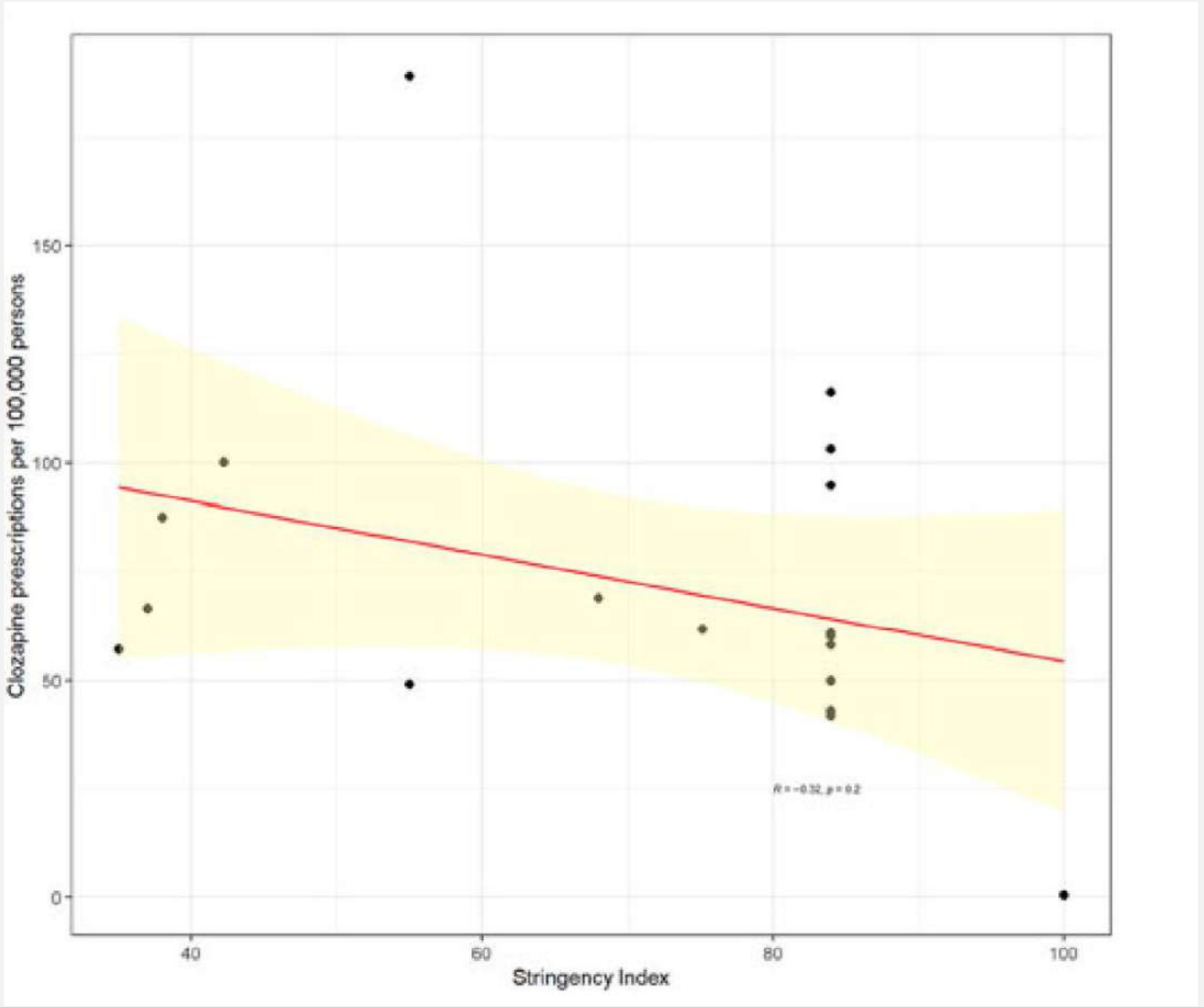


Fig. 1. Choropleth map of clozapine haematological monitoring Stringency Index. Red indicates highest stringency and yellow the lowest stringency. Grey indicates no data.


Health Expenditure per capita
15
10
5
25
50
75
100
Stringency Index
R = 0.43, p = 1.2e-05


Clozapine prescriptions per 100,000 persons
150
100
50
0
40
60
80
100
Stringency Index
R = −0.32, p = 0.2

IS CAPILLARY MONITORING OF CLOZAPINE POSSIBLE?

Original Paper

Point-of-care measurement of clozapine concentration using a finger-stick blood sample

David Taylor[1,2], Matthew Atkins[2,3], Robert Harland[4], Irina Baburina[5], James H MacCabe[6], Salvatore J Salamone[5] and Philip McGuire[6]

Journal of Psychopharmacology
2021, Vol. 35(3) 279–283

DOI: 10.1177/0269881121991567
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SAGE

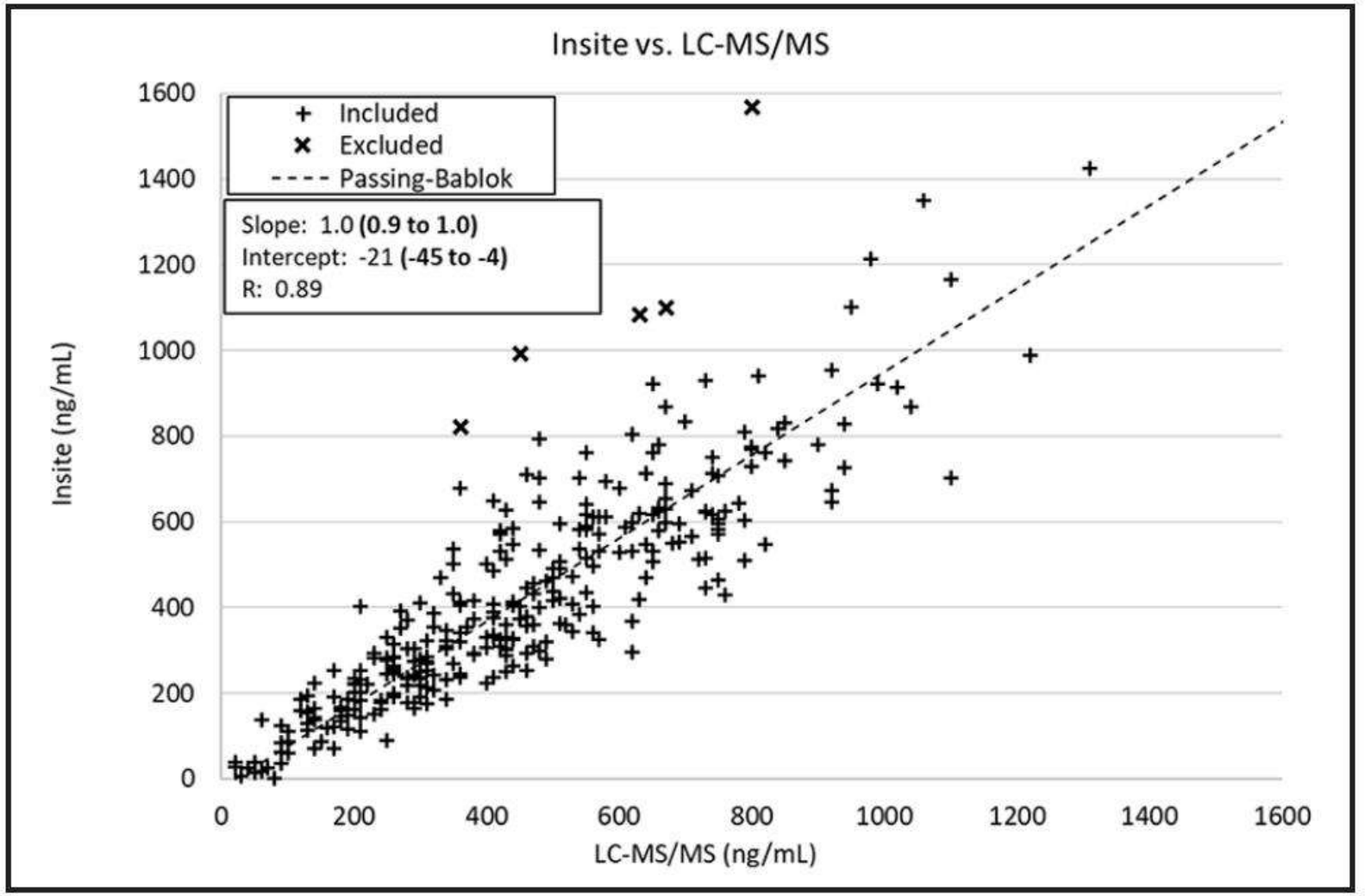


Figure 1. Insite point-of-care testing (capillary whole blood) versus liquid chromatography with tandem mass spectrometry (plasma) concentrations measured. (Excluded (×) $N=5$; Included (+) $N=304$).

Therapeutic Advances in Psychopharmacology *Original Research*

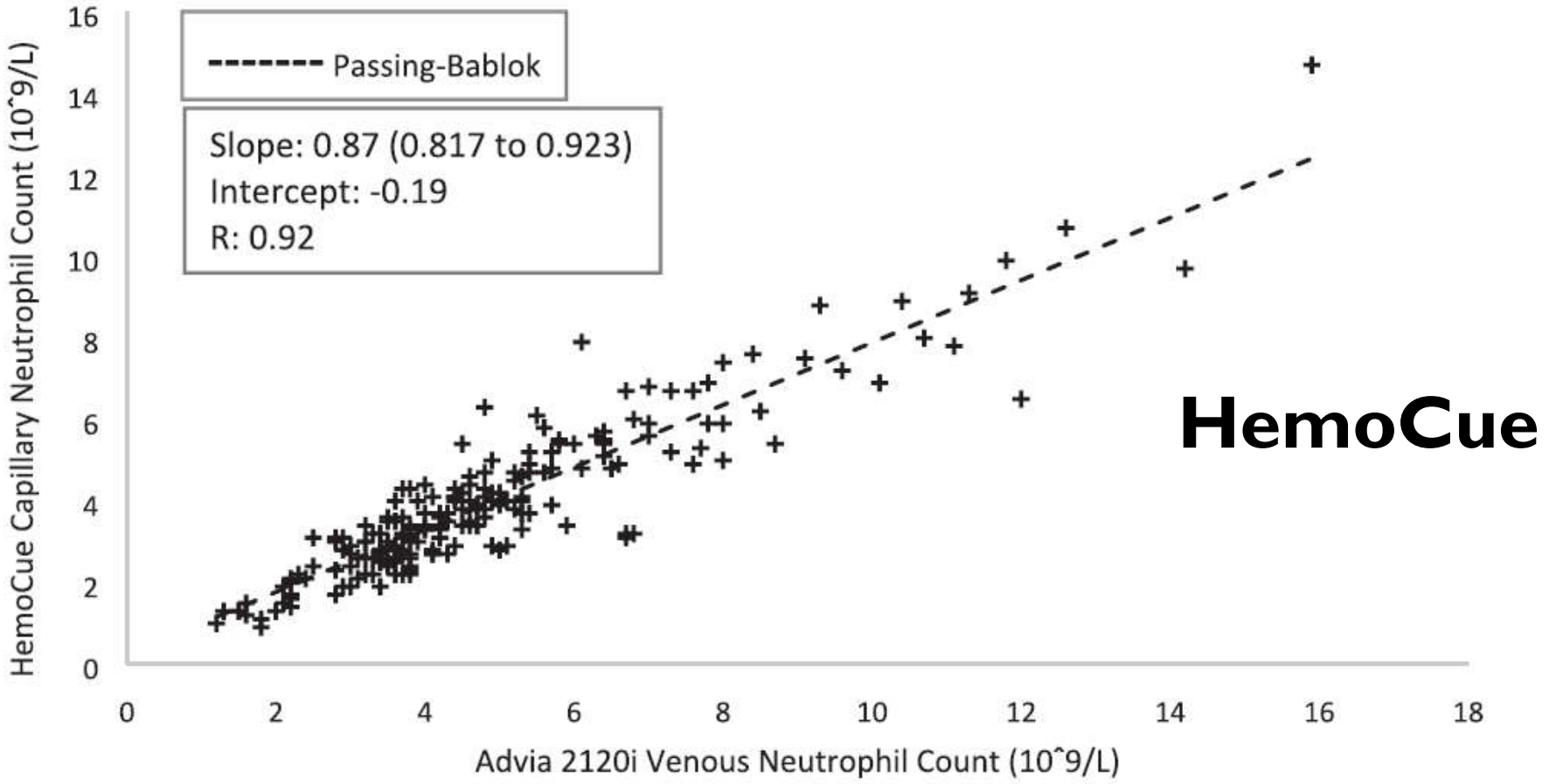
Using a fingerstick test for haematological monitoring in patients treated with clozapine

Matthew Atkins, Philip McGuire, Bhirundra Balgobin, Pravinkumar Patel and David Taylor

Ther Adv Psychopharmacol

2021, Vol. 11: 1–6

DOI: 10.1177/20451253211000865


Passing-Bablok
Slope: 0.87 (0.817 to 0.923)
Intercept: -0.19
R: 0.92
HemoCue Capillary Neutrophil Count (10^9/L)
Advia 2120i Venous Neutrophil Count (10^9/L)
0
2
4
6
8
10
12
14
16
18

HemoCue

Point-of-care haematological monitoring during treatment with clozapine

Figure 2. OLO® Neutrophil (capillary whole blood) versus Advia 2120i (venous whole blood) Neutrophil counts. (N= 215)

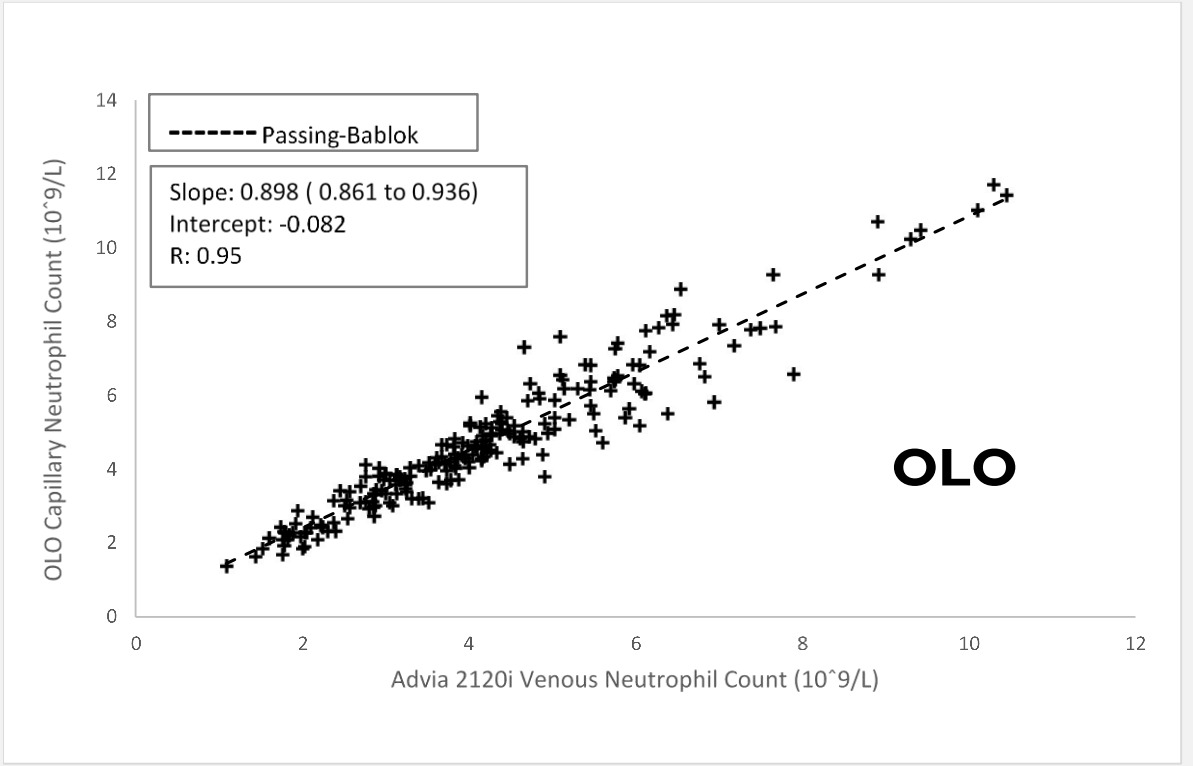
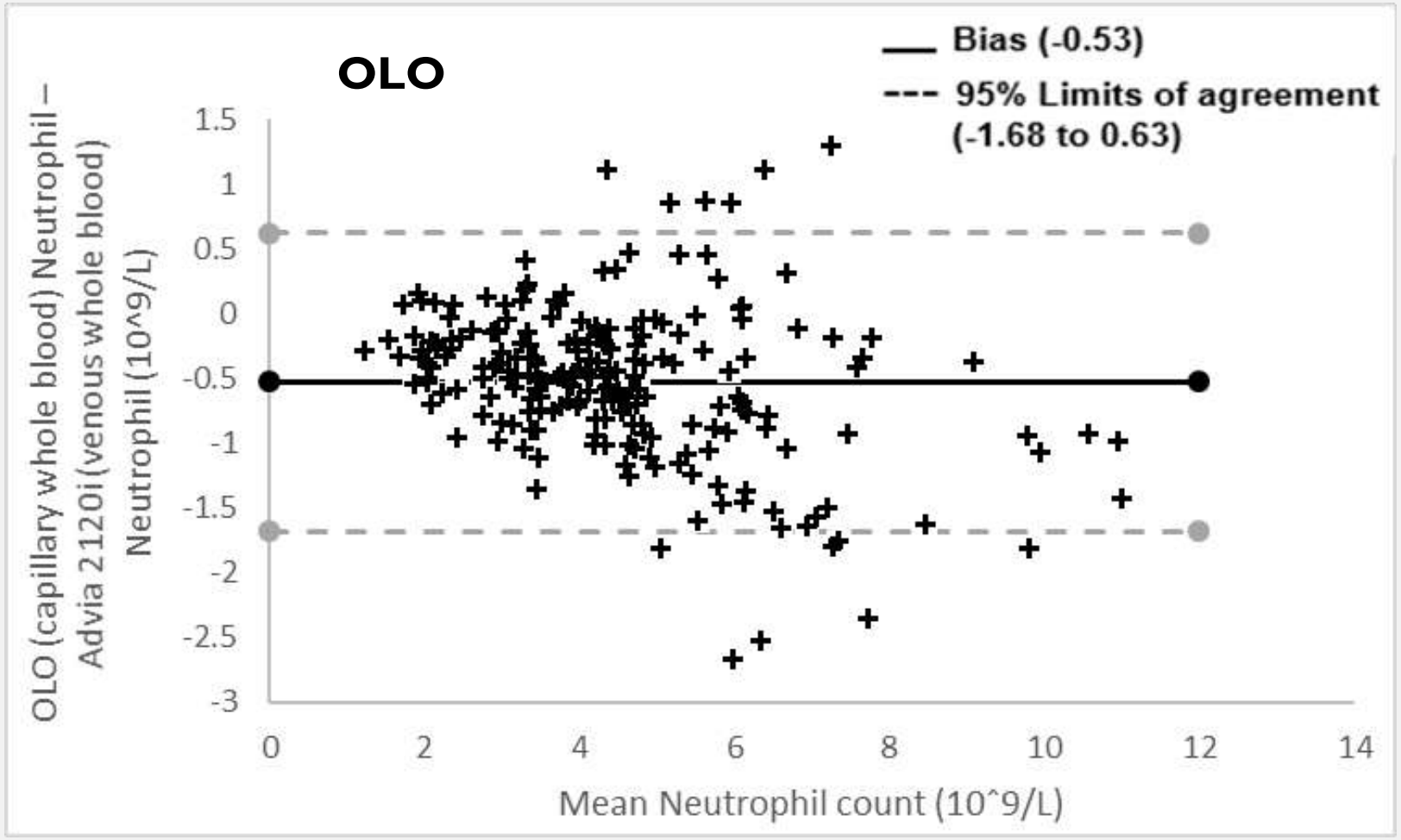


Figure 6. Bland-Altman plot for the difference between OLO capillary whole blood neutrophil count and Advia 2120i venous whole blood neutrophil count against the mean of both methods for neutrophil count. (N= 215)



Journal of Psychiatric Research 157 (2023) 66–71

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journal homepage: www.elsevier.com/locate/jpsychires

Check for updates

Haematological point of care testing for clozapine monitoring

Matthew Atkins [a,b,*], Philip McGuire [b], Bhirundra Balgobin [d], Neville Desouza [a], David Taylor [a,c]

HemoScreen

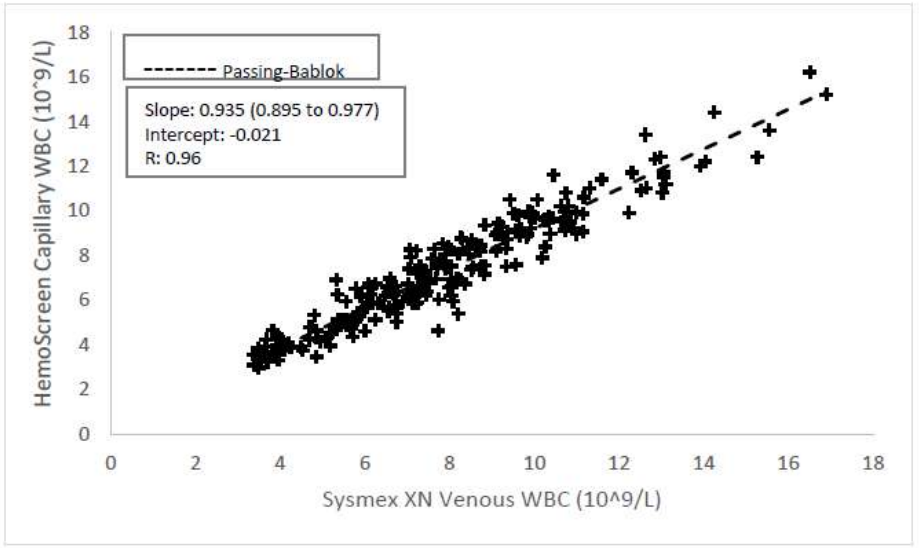

Fig. 1. HemoScreen® WBC (capillary whole blood) versus. Sysmex XN (venous whole blood) WBC counts. (N = 226).

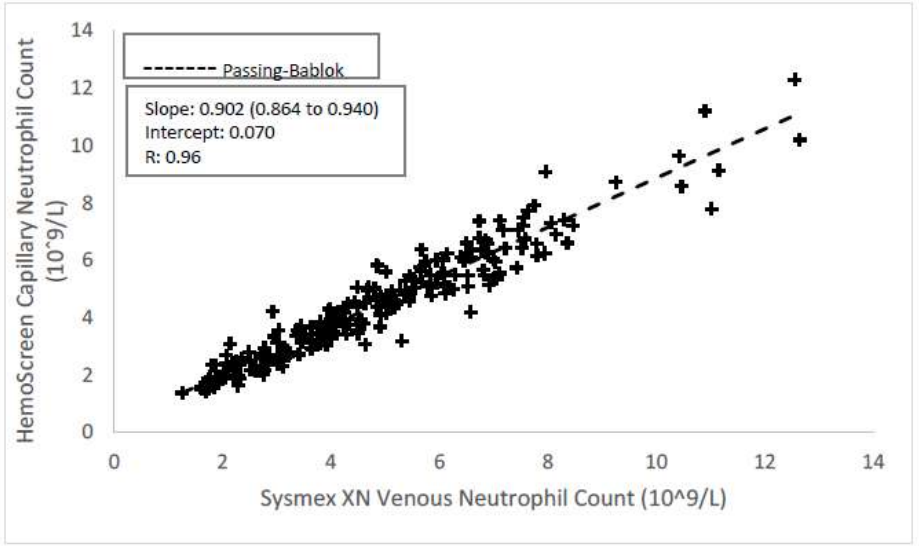

Fig. 2. HemoScreen® Neutrophil (capillary whole blood) versus Sysmex XN (venous whole blood) Neutrophil counts. (N = 226).

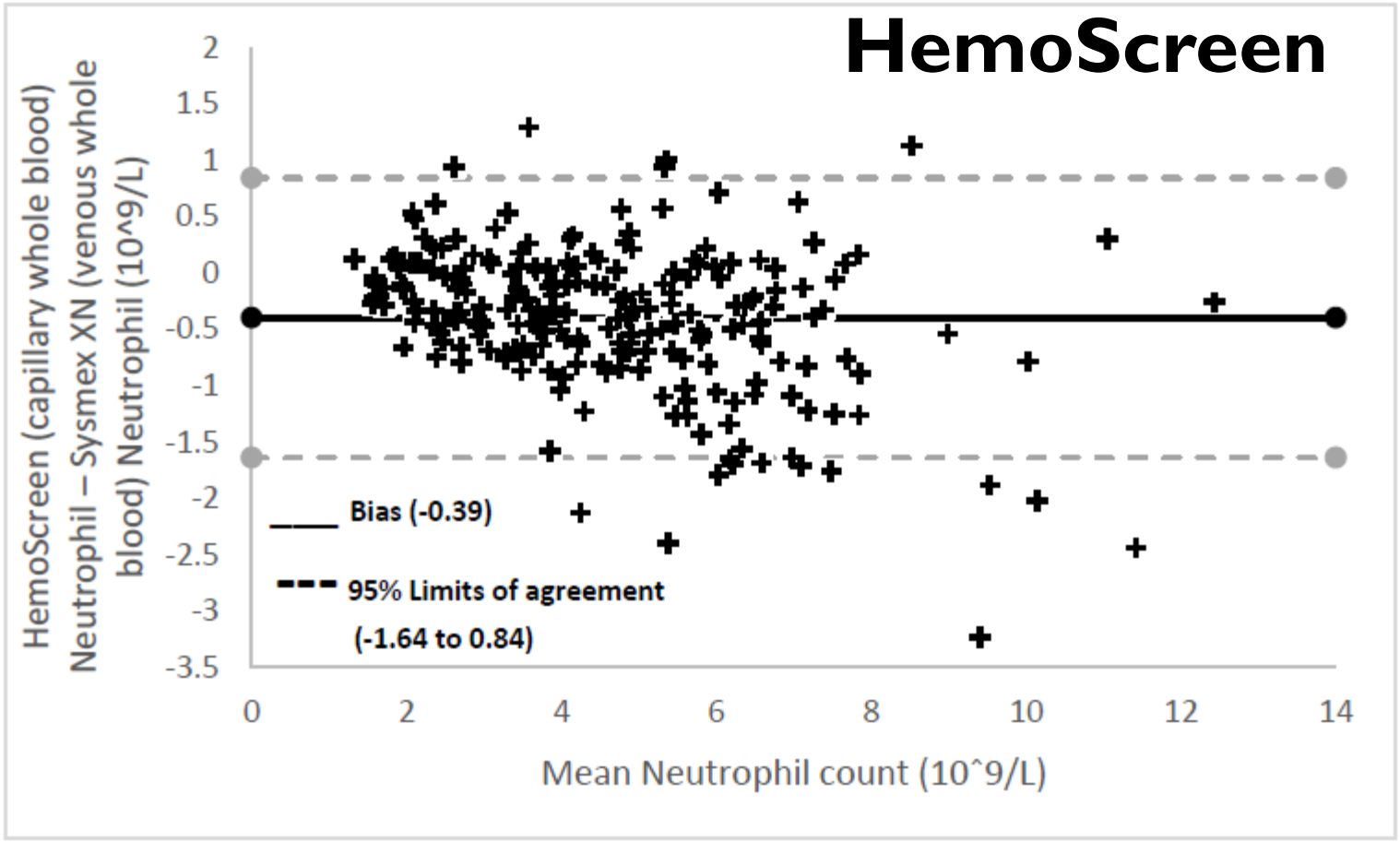

Fig. 8. Bland-Altman plot for the difference between HemoScreen capillary whole blood neutrophil count and Sysmex XN venous whole blood neutrophil count against the mean of both methods. (N = 226).

Psychiatry Research Communications 2 (2022) 100070

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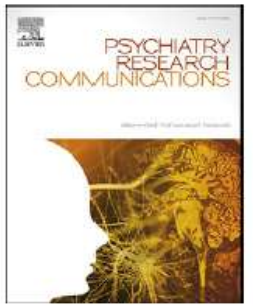


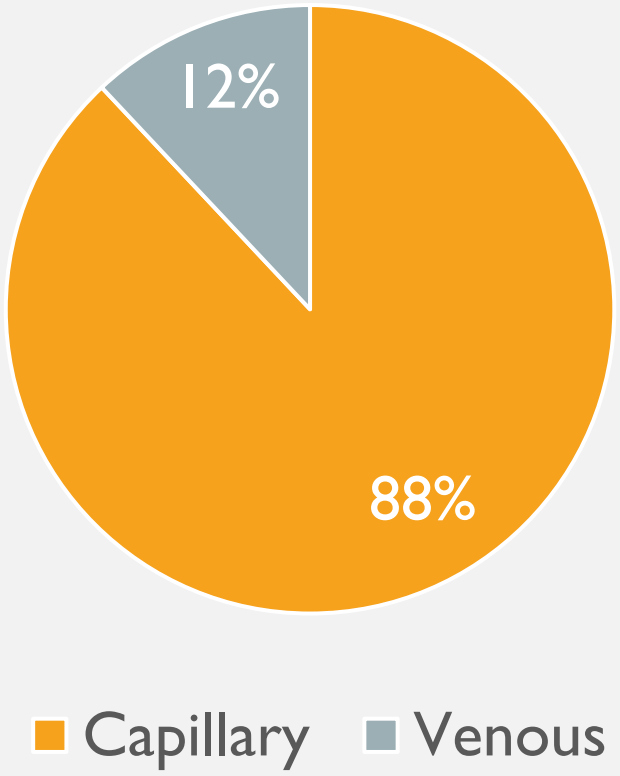
Acceptability of point of care testing for antipsychotic medication levels in schizophrenia

Matthew Atkins [a,b,*], David Taylor [a,b], Robert Harland [a,c], Aaron Brewer [a,c], Sophie Williams [e], Edward Chesney [a,c], Philip McGuire [c,d]

Table 1
Patient sample.

Patients being treated with clozapine	(n = 84)
Male/Female	55/29
Age (years)	47 (21–75)
Duration of clozapine treatment (months)	144 (12–192)
Patients being treated with aripiprazole **(n=22)**	11/11
Male/Female	
Age (years)	30 (20–63)
Duration of aripiprazole treatment (months)	15 months (2 - 36)

PATIENT PREFERENCE



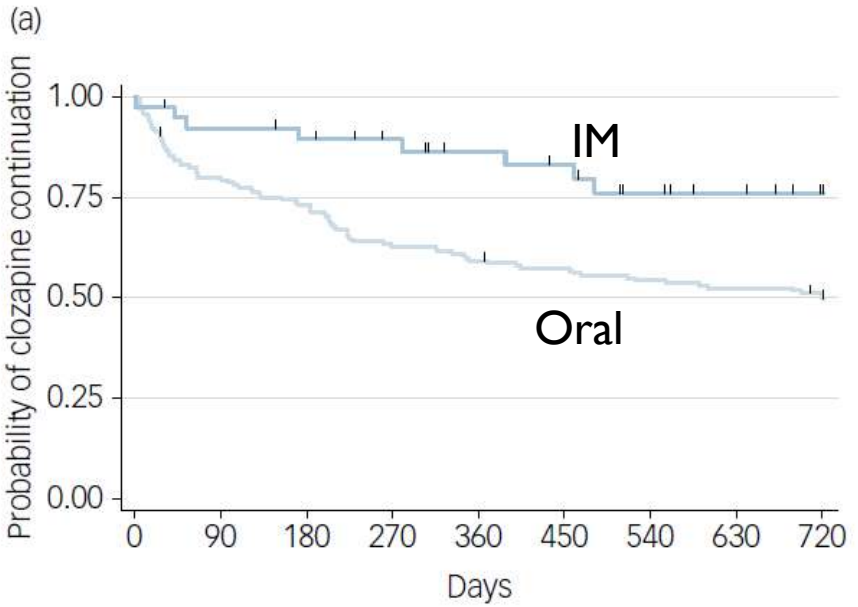
INTRAMUSCULAR CLOZAPINE

BJPsych The British Journal of Psychiatry (2020)
217, 506–513. doi: 10.1192/bjp.2020.115

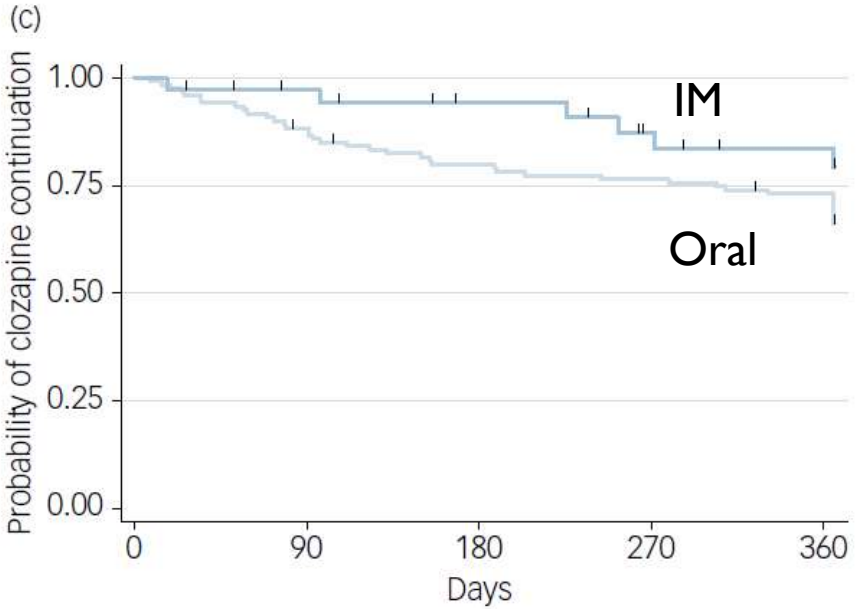
CrossMark

A retrospective study of intramuscular clozapine prescription for treatment initiation and maintenance in treatment-resistant psychosis

Cecilia Casetta, Ebenezer Oloyede, Eromona Whiskey, David Michael Taylor, Fiona Gaughran, Sukhi S. Shergill, Juliana Onwumere, Aviv Segev, Olubanke Dzahini, Sophie E. Legge and James Hunter MacCabe



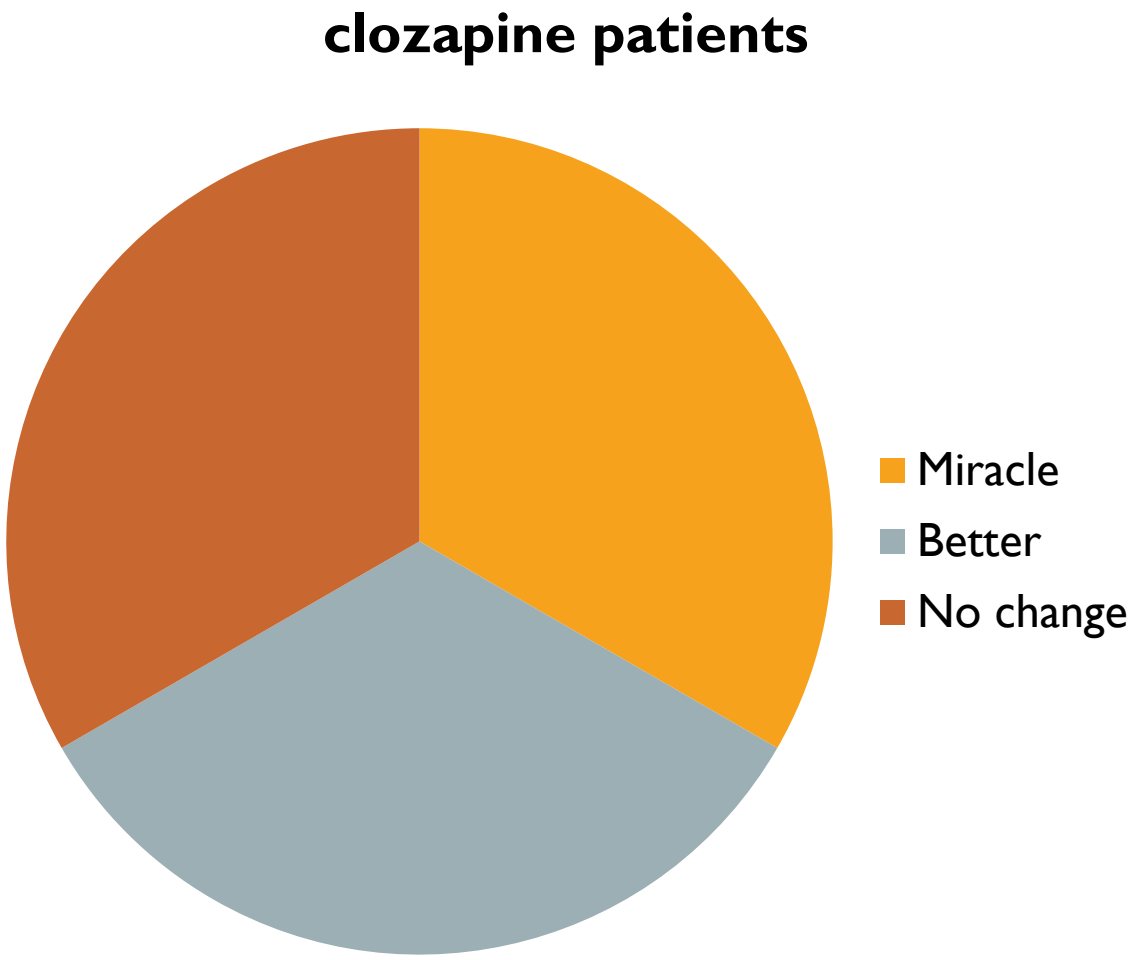
Discontinuation after Rx



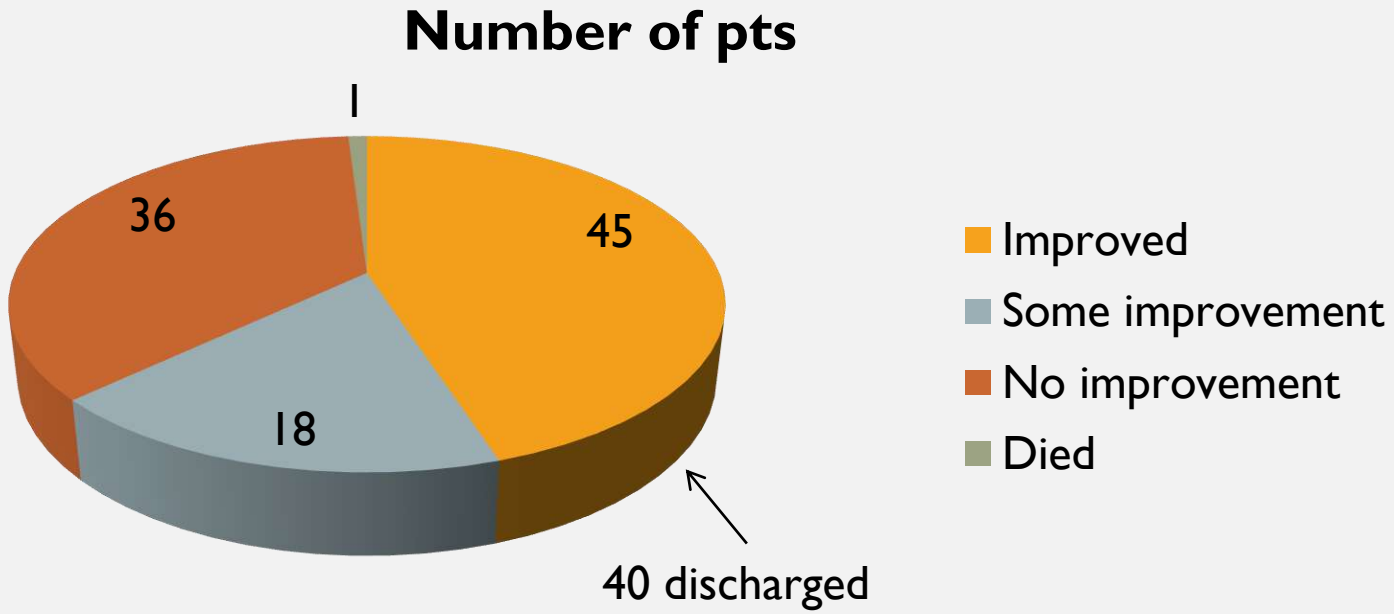
Discontinuation after discharge

WHAT TO EXPECT WITH CLOZAPINE

ROUGH ESTIMATE OF OUTCOME WITH CLOZAPINE



N=100
LONG-STAY REFRACTORY PATIENTS



Wilson & Claussen 1995

AGRANULOCYTOSIS

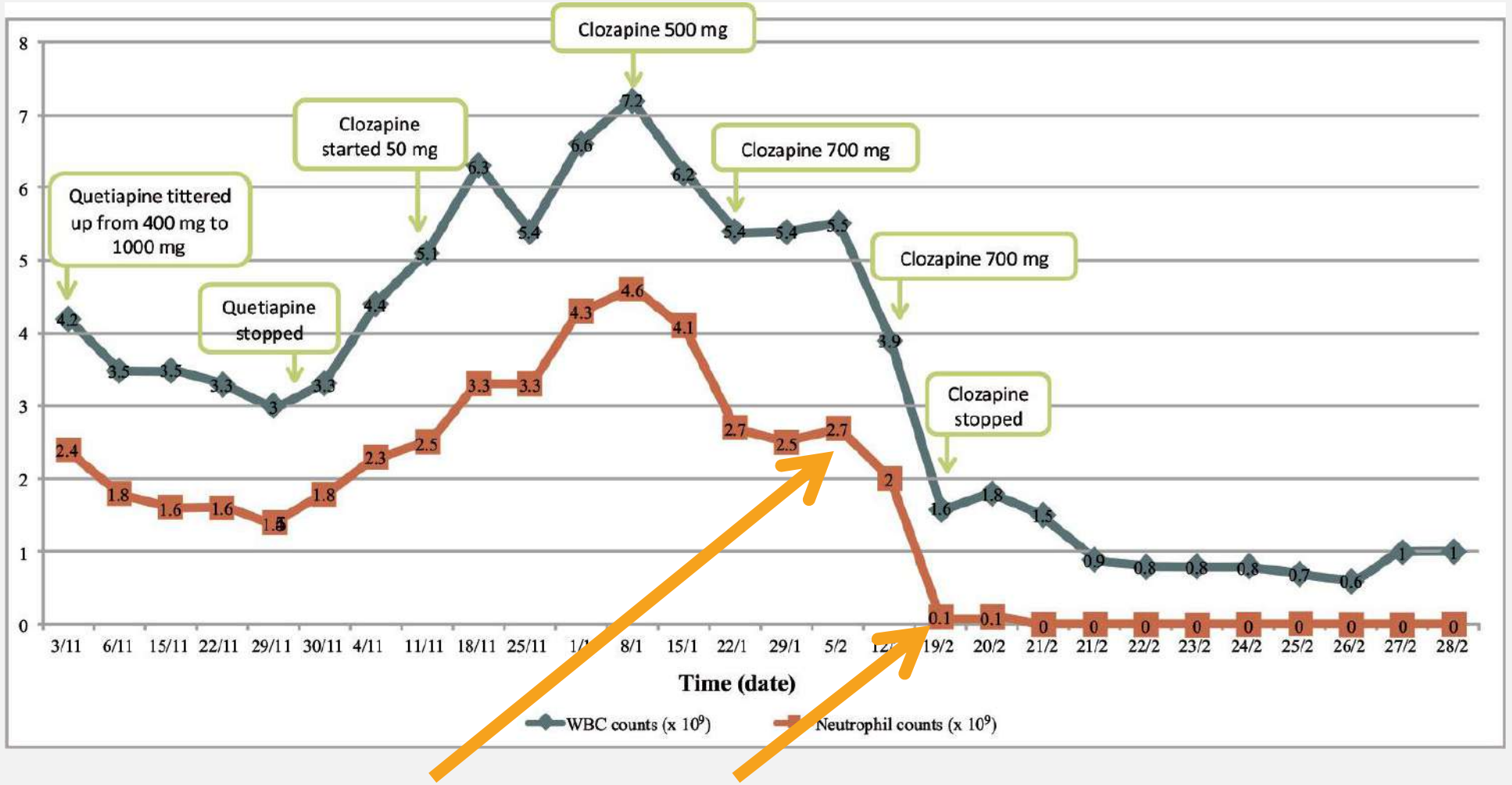
RISK OF AGRANULOCYTOSIS

(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

Relaxation of the criteria for entry to the UK Clozapine Central Non-Rechallenge Database: a modelling study

Ebenezer Oloyede, Eromona Whiskey*, Cecilia Casetta, Olubanke Dzahini, Danielle Dunnett, Shreyans Gandhi, Fiona Gaughran, Sukhi Shergill, Philip McGuire, James H MacCabe†, David Taylor†*

Summary

Background Clozapine is uniquely effective in treatment-resistant psychosis. In the UK, patients must discontinue clozapine indefinitely if they are placed on the Central Non-Rechallenge Database (CNRD) after their haematological parameters fall below particular thresholds. Under exceptional circumstances, patients can be rechallenged on clozapine under an off-licence agreement. In the USA in 2015, restrictive practice was discontinued to allow greater flexibility for clozapine maintenance. The absolute neutrophil count leading to treatment interruption was lowered from less than $1{\cdot}5\times10^9$/L to less than $1{\cdot}0\times10^9$/L and platelet and white cell count monitoring were ceased. We aimed to investigate the implications of a similar policy change on clozapine use in the UK.

Methods This was a modelling study of all patients registered on the UK CNRD. First, we determined the proportion of patients placed on the database in the UK who would have had to discontinue clozapine treatment under the US Food and Drug Administration (FDA) criteria. Second, we compared the haematological characteristics of patients who did or did not meet FDA criteria for discontinuing clozapine, including the time to registration from clozapine initiation and the proportion of cases of severe neutropenia at registration. Third, we investigated the success rates of clozapine re-challenge for patients that had been placed on the CNRD. Successful rechallenge was defined as no recurrence of CNRD registration.

Findings Between May 2, 2002 and March 1, 2021, 3731 patients were placed on the CNRD, with a mean age of 47 years (SD 15), including 1420 (38%) women and 2311 (62%) men, of whom 3089 (83%) were White, 360 (10%) were Black, 190 (5%) were Asian, and 92 (2%) were classified as other. 566 (15%) of 3731 patients met the equivalent criteria for clozapine discontinuation under the FDA guidelines. The median time to CNRD registration from clozapine initiation was 1·6 years (IQR 0·2–4·9). Data for 519 rechallenged patients were examined; 419 (81%) were successful. Clozapine rechallenge success rates were broadly similar between individuals who did not meet the US CNRD registration criteria (36 [78%] of 46) and those who did meet the criteria (383 [81%] of 473).

Interpretation Implementing the revised FDA monitoring criteria in the UK would substantially reduce clozapine discontinuation for haematological reasons, which would greatly improve the mental health outcomes of these patients without having a major effect on their physical health.

Funding None.

Lancet Psychiatry 2022

Published Online
June 27, 2022
https://doi.org/10.1016/S2215-0366(22)00188-2

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†Joint last authors

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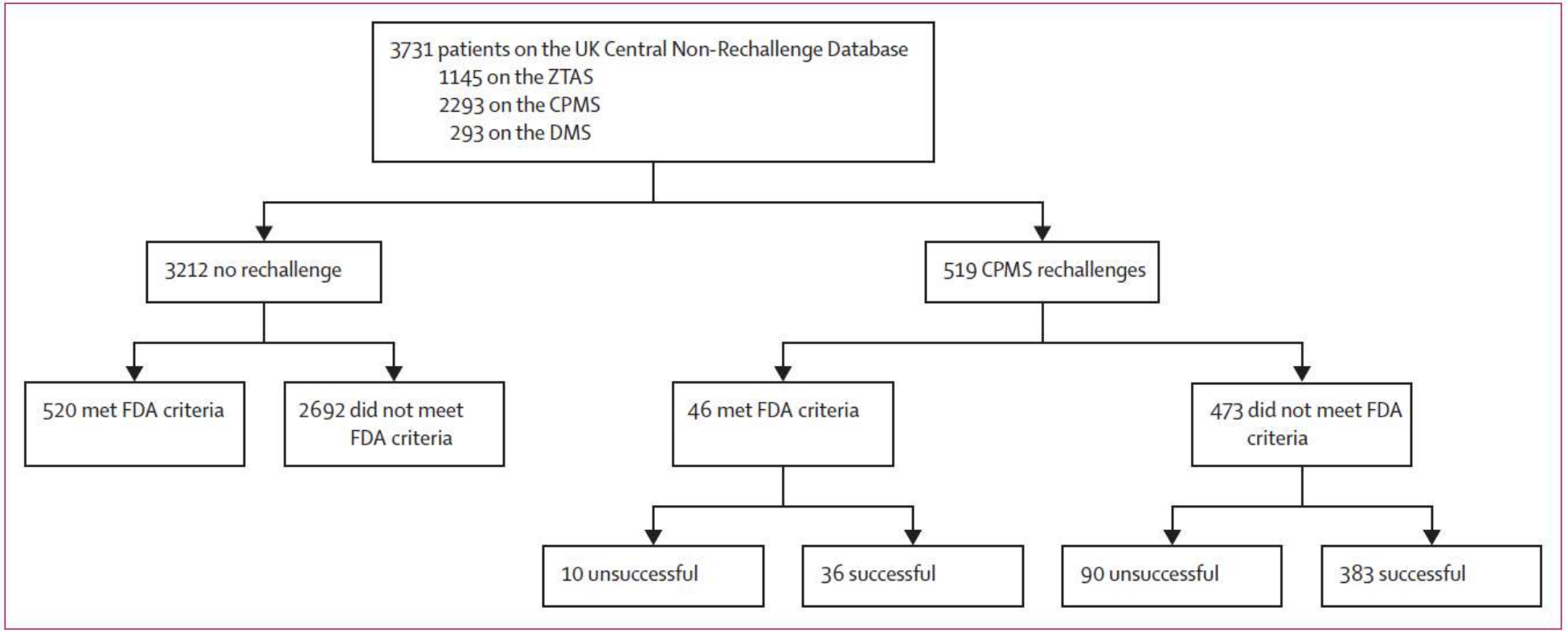

3731 patients on the UK Central Non-Rechallenge Database
1145 on the ZTAS
2293 on the CPMS
293 on the DMS
3212 no rechallenge
519 CPMS rechallenges
520 met FDA criteria
2692 did not meet FDA criteria
46 met FDA criteria
473 did not meet FDA criteria
10 unsuccessful
36 successful
90 unsuccessful
383 successful

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

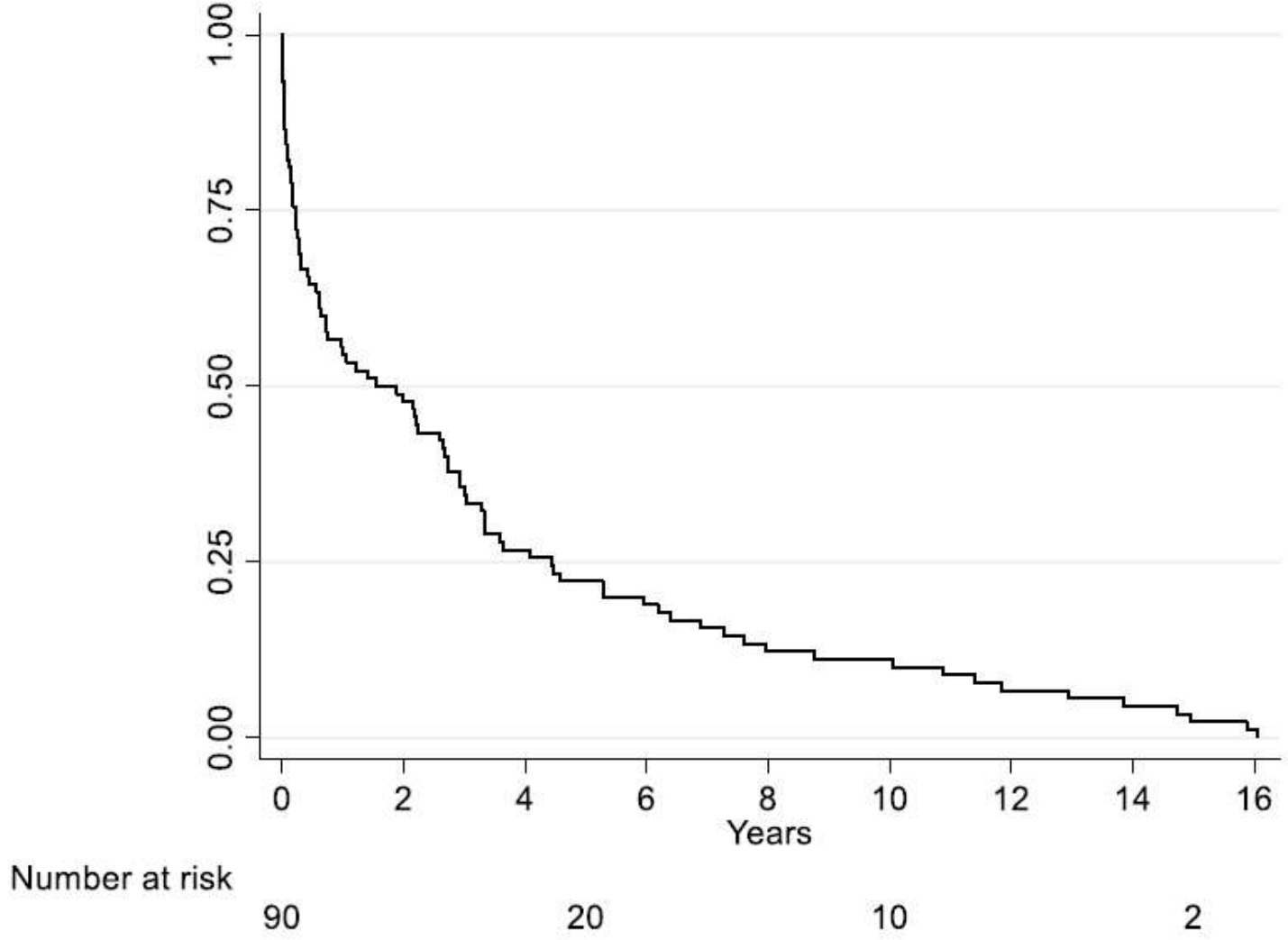


Fig. 1 Kaplan Meier for the time to BEN registration from clozapine initiation

CLOZAPINE GENETIC TESTING

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%**

AGRANULOCYTOSIS

Best sensitivity	**54%**
Best specificity	**99%**

AGRANULOCYTOSIS – HLA VARIANTS

Best sensitivity **54%** (only half of cases have the variant)

Best specificity **99%** (a high proportion of the people with the variant get agranulocytosis)

Explanations:

There is more than one genetic cause of agranulocytosis

The defined phenotype is polluted (not everybody with ‘clozapine-induced agranulocytosis’ has clozapine-induced agranulocytosis)

Schizophrenia

ARTICLE OPEN

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.

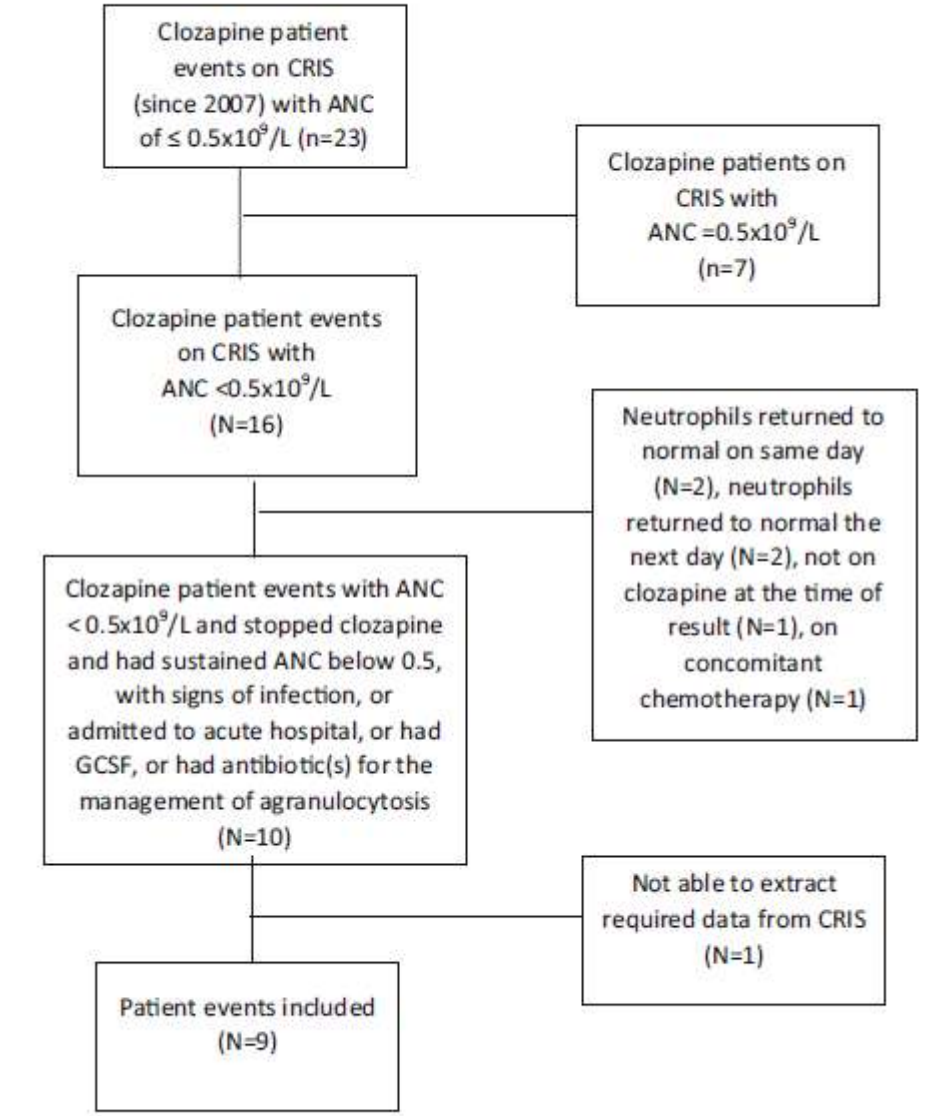
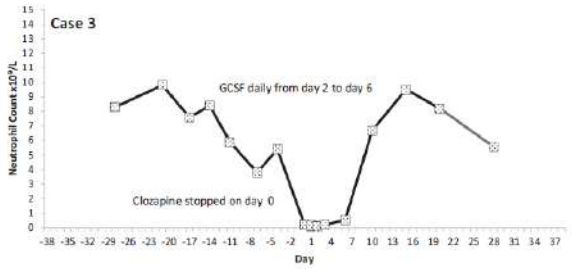
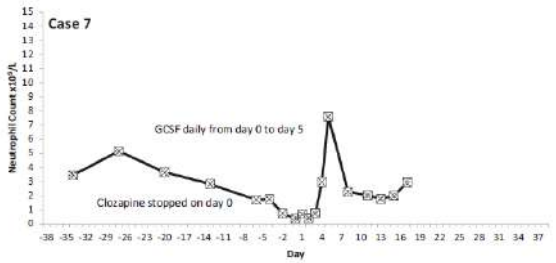
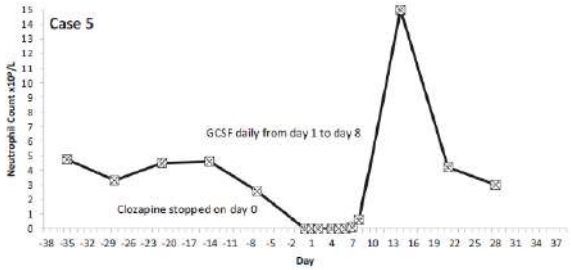


Fig. 1 Case selection.


Case 3
Neutrophil Count x10^9/L
GCSF daily from day 2 to day 6
Clozapine stopped on day 0
Day


Case 7
Neutrophil Count x10^9/L
GCSF daily from day 0 to day 5
Clozapine stopped on day 0
Day


Case 5
Neutrophil Count x10^9/L
GCSF daily from day 1 to day 8
Clozapine stopped on day 0
Day

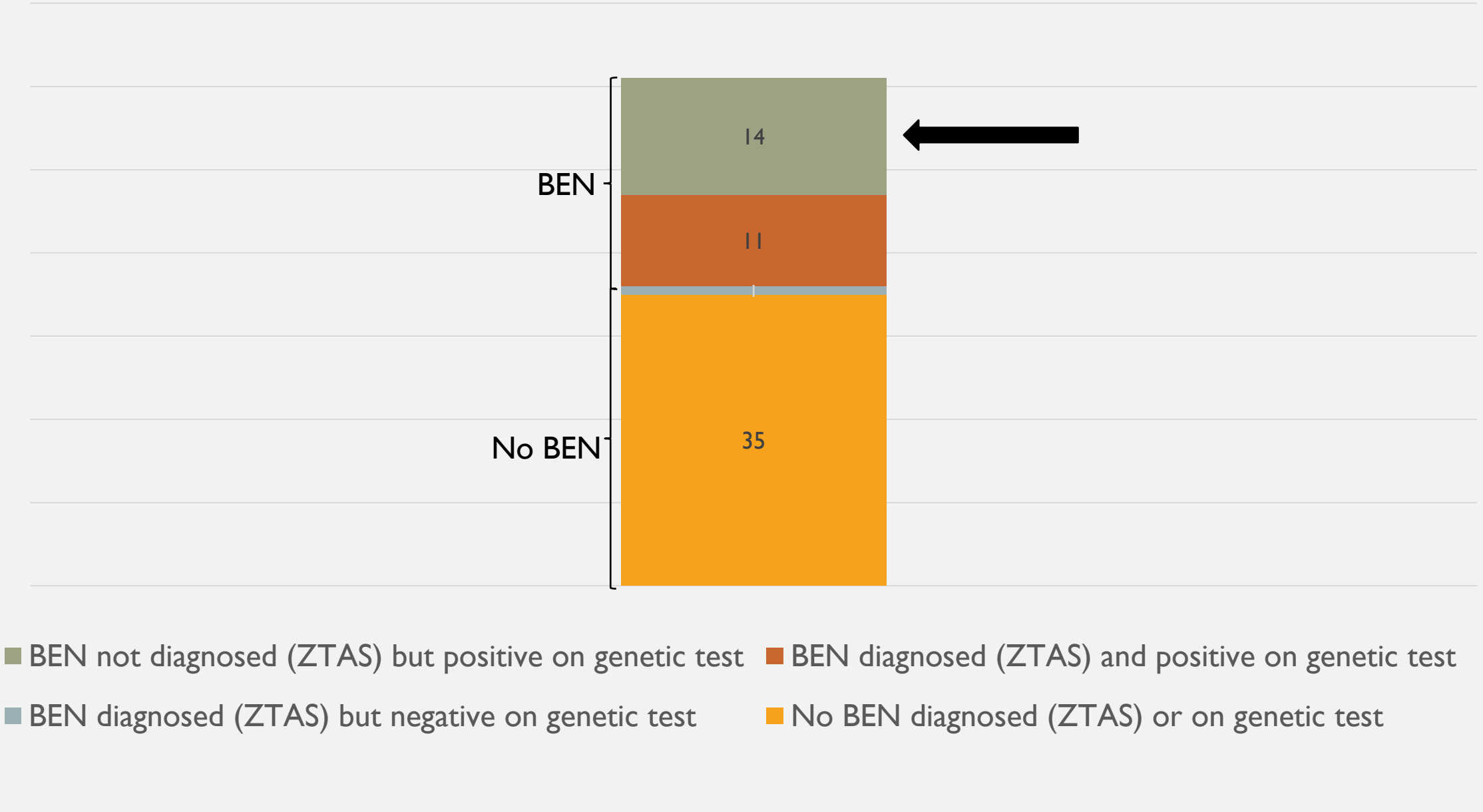
BENIGN ETHNIC NEUTROPENIA

- 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)).

BENIGN ETHNIC NEUTROPENIA

MAUDSLEY STUDY

- 70 patients tested at random in clozapine clinic
- 10 previously registered as BEN
- 14 more found to have BEN via genetic test


14
11
35
BEN
No BEN
BEN not diagnosed (ZTAS) but positive on genetic test
BEN diagnosed (ZTAS) and positive on genetic test
BEN diagnosed (ZTAS) but negative on genetic test
No BEN diagnosed (ZTAS) or on genetic test

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).

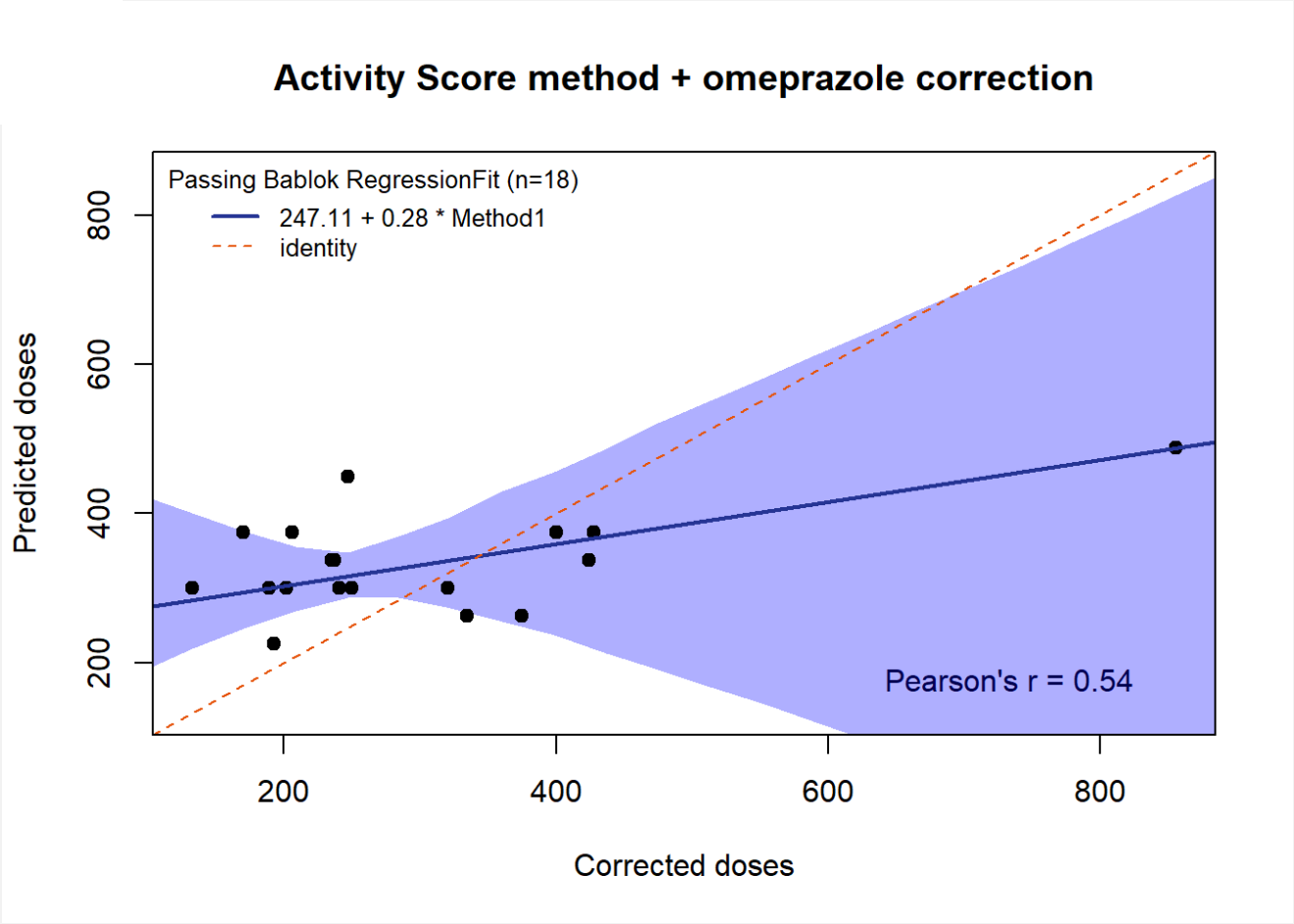
Predicting clozapine dose required to achieve a therapeutic plasma concentration – A comparison of a population algorithm and three algorithms based on gene variant models

Psychopharm

Journal of Psychopharmacology
1–10

DOI: 10.1177/02698811231199104
journals.sagepub.com/home/jop
Sage

David Taylor[1], Caroline Cahill[2], Paul Wallang[2,3], Louise Millard[2], Luis Ramudo Cela[4] and Kieran C Breen[2]



Mean difference between predicted dose and actual dose = 31mg/day

Based on activity of CYP1A2, CYP3A4, CYP3A5 genes, *NFIK* rs28379954

Predicting dose to give 350mg/L (n=18);

Genetic Analysis of Clozapine Metabolism in a Patient With Subtherapeutic Clozapine Plasma Concentrations—The Importance of CYP3A5

A Case Report

Okon-Rocha, Ramudo-Cela, Taylor

TABLE 2. Clozapine and Norclozapine Levels During Hospitalization

Treatment Regime-Clozapine Dose Daily	Date	Clozapine Plasma Concentration, mg/L	Norclozapine Plasm Concentration, mg/L
450 mg	17/08/2020	0.25	0.15
550 mg	14/09/2020	0.27	0.11
550 mg + cariprazine 1,5 mg	14/10/2020	0.42	0.19
625 mg + cariprazine 3 mg	02/02/2021	0.36	0.16
725 mg + cariprazine 3 mg	17/03/2021	0.35	0.17
825 mg + cariprazine 3 mg	25/05/2021	0.41	0.20
850 mg + amisulpride 200 mg + cimetidine 800 mg	31/08/2021	0.93	0.41
800 mg + amisulpride 100 mg + cimetidine 400 mg	13/09/2021	0.76	0.33
800 mg + amisulpride 100 mg + cimetidine 400 mg	21/12/2021	0.74	0.36

All samples were taken 10–14 hours after dose.

All samples taken when the patient was in hospital.

PANSS SCORES

BEFORE CIMETIDINE	AFTER CIMETIDINE
111	47

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.

STUFF WE SHOULD BE DOING…

- Capillary TDM
- Capillary neutrophils
- Genetic testing
- Using clozapine more

Saudi Pharmaceutical Journal 31 (2023) 214–221

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Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Patients' and primary carers' views on clozapine treatment for schizophrenia: A cross-sectional study in Qatar

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ARTICLE INFO

Article history:
Received 11 May 2022
Accepted 10 December 2022
Available online 16 December 2022

Keywords:
Clozapine
Schizophrenia
Side effects
Subjective experience
Qatar

ABSTRACT

Subjective views of clozapine treatment among patients with schizophrenia in the Middle East and North African MENA Region have not previously been assessed. Globally, few studies have assessed the views of carers to clozapine treatment. We conducted a cross-sectional survey, using a clinician administered structured interview, of patients with schizophrenia/schizoaffective disorder prescribed clozapine in Qatar, and their primary carers. Participants were asked to rate clozapine against prior their antipsychotic treatment in terms of specific benefits and side effects. Forty-two patients and 33 carers participated in the study. Of the patients, two thirds were male, approximately half were Qatari and the mean age was 33.9 years. Patients and carers rated clozapine as superior to prior antipsychotic treatment on all 7 potential benefits inquired about. The greatest perceived benefit was improved mood. Patients rated clozapine as less likely to cause extrapyramidal side effects but more likely to cause 18 other potential side effects compared to prior antipsychotic treatment, with the greatest difference being for nocturnal salivation, increased appetite, and constipation. Nearly half of patients (48 %) and two thirds of carers (64 %) stated that they would have preferred to start clozapine earlier in their illness. Sixty percent of patients and 37 % of carers regarded the information that they had received from health professionals on clozapine as inadequate. Less than half of patients and approximately-two thirds of carers had adequate knowledge of haematological monitoring for clozapine. Generally, there were significantly positive correlation between patients and carers regarding the overall side effects of clozapine treatment. Likewise, improvement in hearing voices paranoid thoughts correlated with improved quality of life. In summary, the results show that patients and carers appreciate the benefits of clozapine despite its side effects being problematic. The results support clozapine being offered earlier in treatment and services providing more information on clozapine to patients and carers.

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