Using Clozapine

How early is too soon?

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Objectives

Following this presentation, participants will be able to:

- Evaluate the efficacy and effectiveness of Clozapine for treatment resistant schizophrenia (TRS)
- Consider the use of Clozapine during the early phase of schizophrenia
- Develop expertise in using Clozapine in routine care

TREATMENT RESISTANCE

What is the Definition of TRS?

- Howes et al, 2016:
  - Failure to respond to ≥2 past treatment episodes with different antipsychotic drugs and at least one LAI (for at least 4 months)
  - At least moderate severity and <20% symptom reduction during a prospective trial or observation of ≥6 weeks
  - After treatment onset: early onset (within 1 y), medium-term onset (1–5 y), late onset (>5 years)
- Kane et al, 1988:
  - Patients who failed to respond to 2 trials
  - No period of good functioning for ≥ 5 years
  - BPRS ≥ 45 , including two among hallucinations, suspiciousness, conceptual disorganisation, unusual thought content with ratings ≥ 4
  - CGI ≥ 4
- Kane et al, 2001 - partial or poor response to:
  - 2 trials with ≥ 600 mg CPZ equivalents for ≥ 6 weeks PLUS
  - 1 ADDITIONAL trial with ≥ 200 and < 500 mg CPZ equivalents for ≥ 6 weeks
  - BPRS item scores ≥ 4 on one of the following items: hallucinations, suspiciousness, conceptual disorganisation, or unusual thought content
- Other definitions were proposed: no consensus!

Howes OD, et al. AJP. 2016;174(3):216-229. doi:10.1176/appi.ajp.2016.16050503.
Kane J, et al. Arch Gen Psychiatry. 1988;45(9):789–796, Kane JM, et al. Arch Gen Psychiatry. 2001;58(10):965-972, Vanelle JM. European Psychiatry. 1997;12:321s-326s.

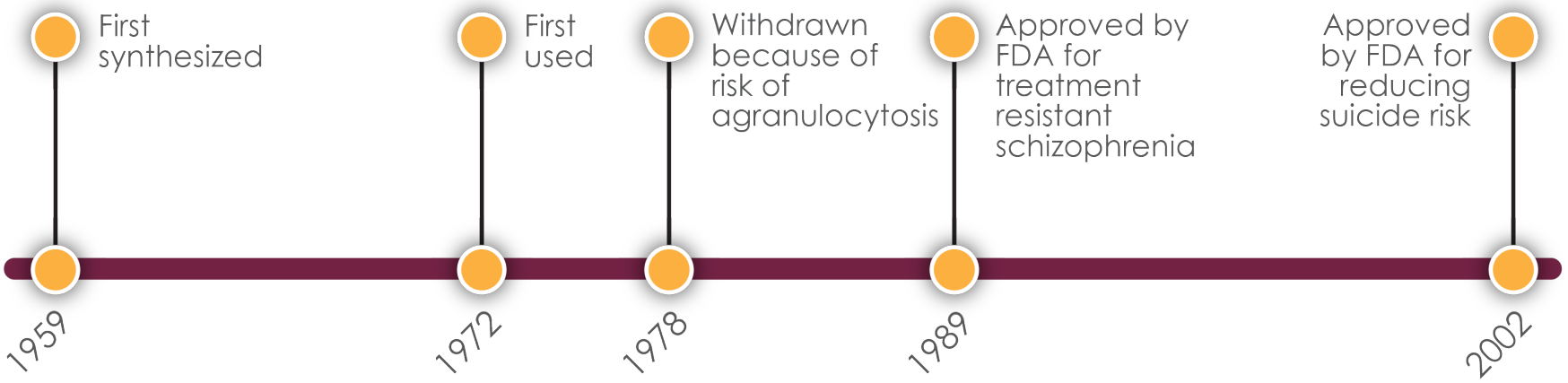
Occurrence of Treatment Resistance

- Kane et al, 1988
  - 20 – 30% become TR after a period of response during the first two years of treatment
- Manchanda et al, 2005
  - 15.1% of FEP patients showed persistent TR during the first two years of treatment
- NICE, 2010
  - Up to 40% of patients will not respond favourably "despite the sequential use of the recommended doses for 6 to 8 weeks of at least two antipsychotics"
- Agid et al, 2011
  - 50/327 patients with FEP (15%) did not respond to two consecutive antipsychotic trials (OLZ/RISP)

Kane J, et al. *Arch Gen Psychiatry*. 1988;45(9):789-796. NICE (2010). NICE clinical guideline 82. Department of Health, London, UK. Manchanda R, et al. *Schizophrenia Research*. 2005;80(1):113-116. Agid O, et al. *The Journal of Clinical Psychiatry*. 2011;72(11):1439-1444.

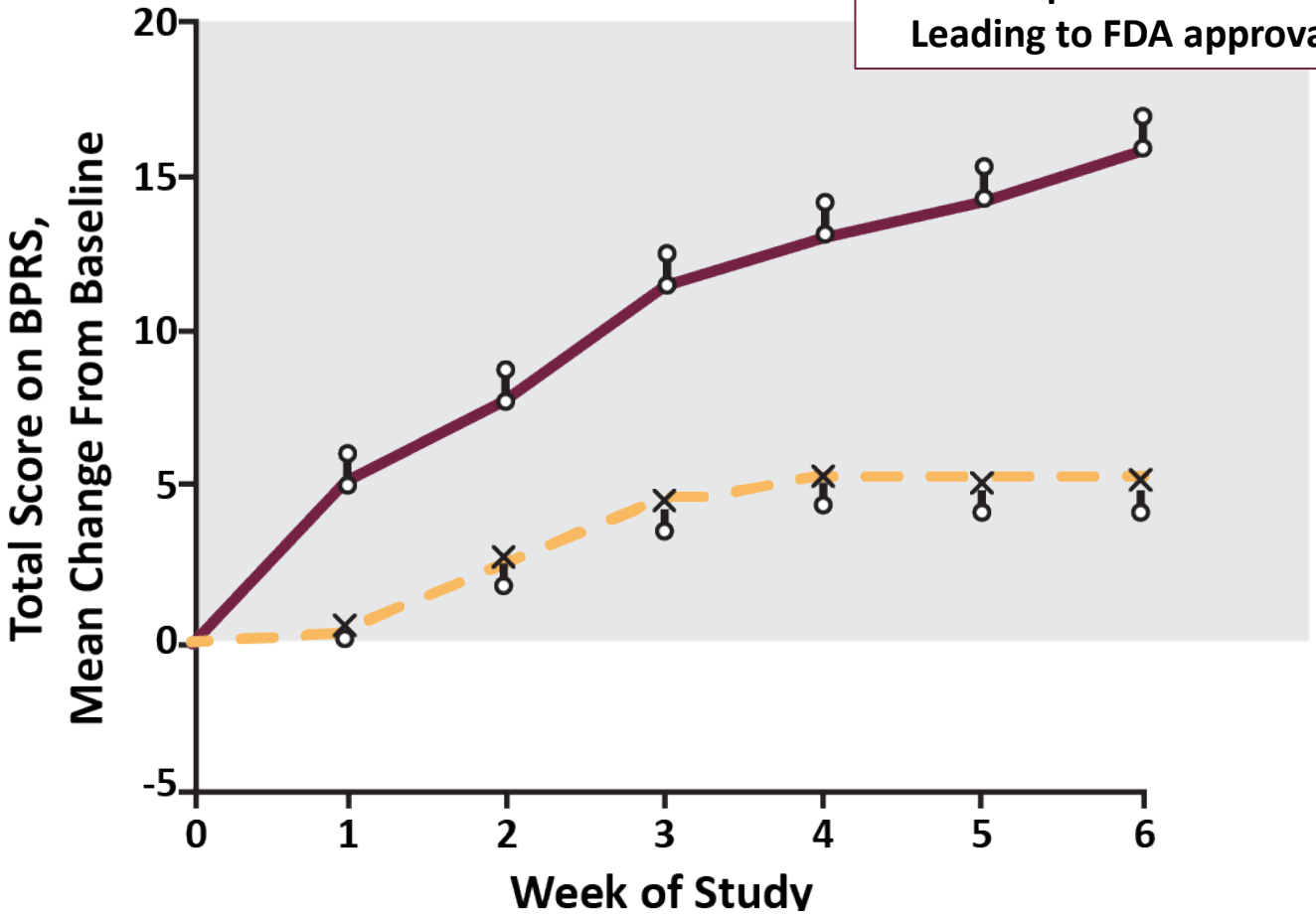
HOW EFFICIENT IS CLOZAPINE?

The History of Clozapine



The Evidence for Clozapine – Better Efficacy in TRS

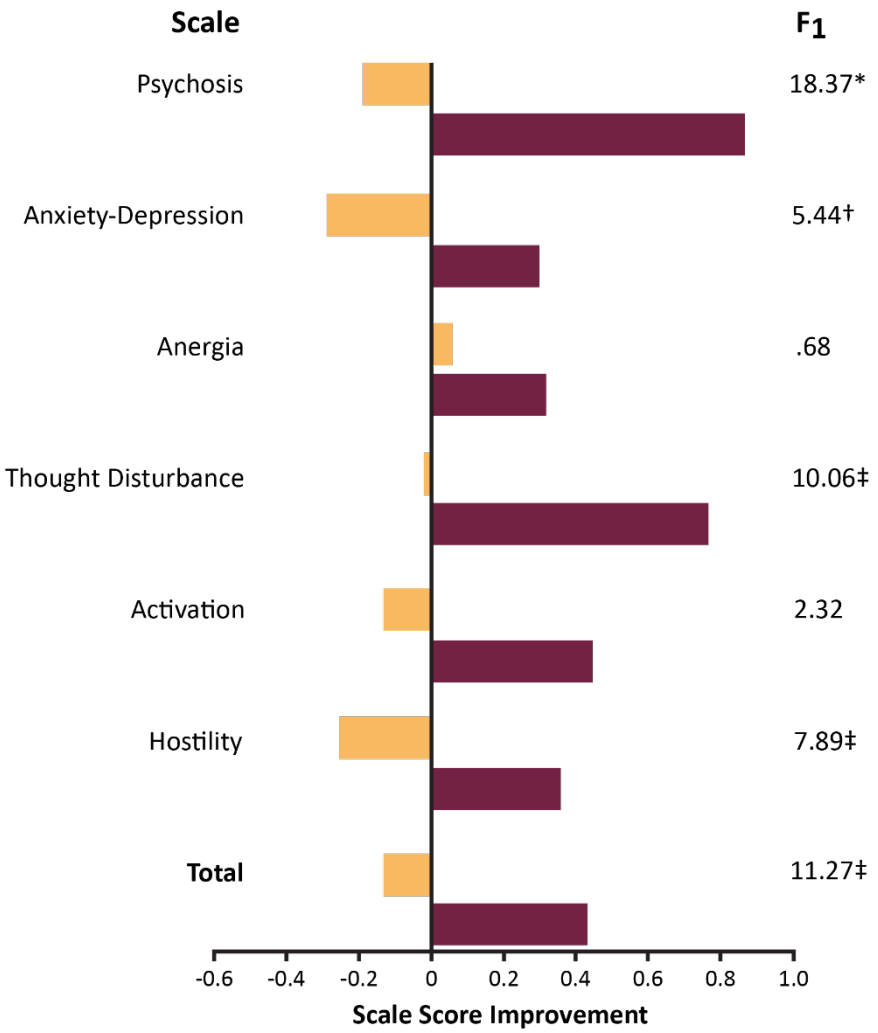
4% response with Chlorpromazine (n=139)
30% response with Clozapine (n=126)
Leading to FDA approval of Clozapine



Mean TOTAL BPRS change from baseline. P<.001 during each week of study.

Kane J, et al. *Arch Gen Psychiatry*. 1988;45(9):789–796.

Is Clozapine Efficacy Confined to Very Severe TRS?



57% response rate with Clozapine
12% discontinuation with Clozapine
N = 36 Clozapine

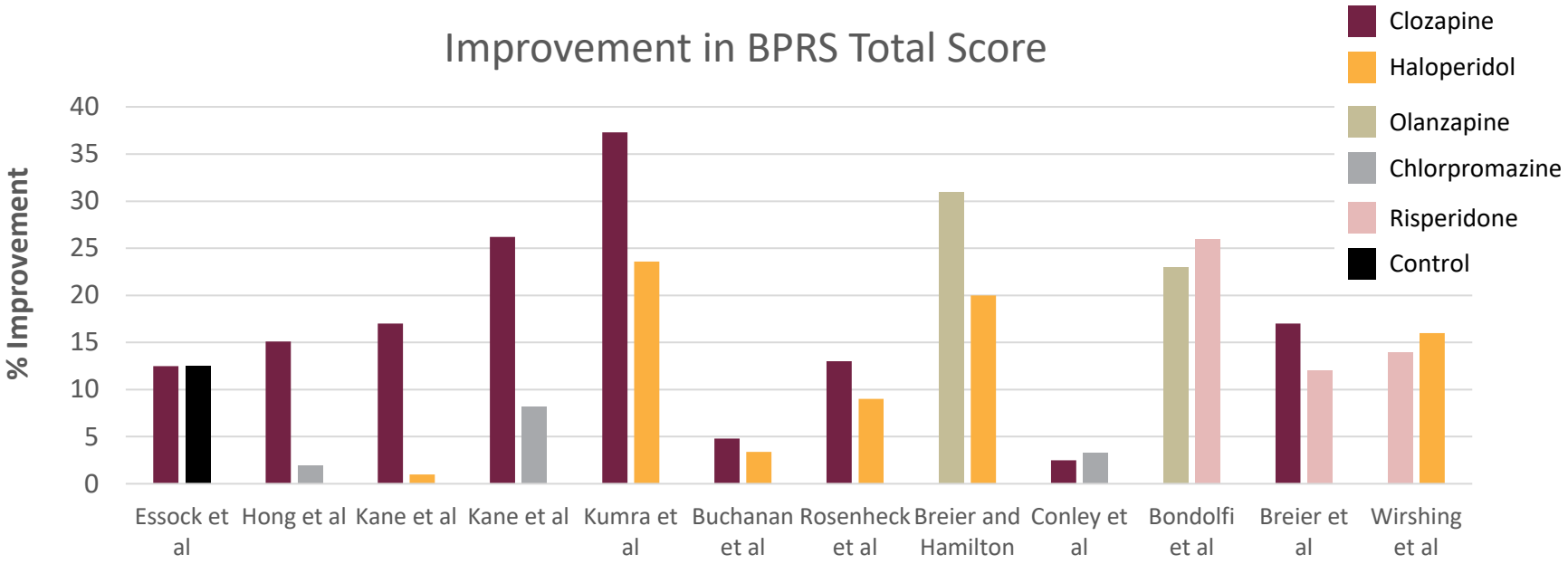
25% response rate with Haloperidol
51% discontinuation with Haloperidol
N = 34 Haloperidol

Scale score improvement from baseline to final rating for Brief Psychiatric Rating Scale subscales and total score for all randomized subjects. All subscales are displayed using change based on a 7-point scale to allow meaningful comparisons.
$^{*}P<.001$; $^{\dagger}P<.05$; $^{\ddagger}P<.01$

Kane JM, et al. *Arch Gen Psychiatry*. 2001;58(10):965-972.

Meta-analysis of FEP and Clozapine in TRS (Chakos et al, Am J Psych 2001)

- Meta-analysis of 12 RCTs in TRS
- Greater reduction in symptoms with clozapine vs. typical antipsychotics
- Other SGAs did not share this superiority

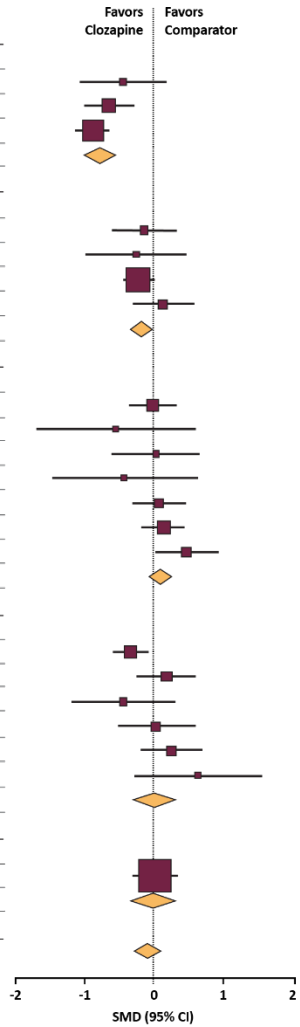


Chakos M, et al. *Am J Psychiatry*. 2001;158(4):518-26.

Recent Meta-analysis of Antipsychotics in TRS (Samara et al, JAMA Psy 2016)

Pairwise Meta-analysis of All Clozapine Trials per Comparator Drug

Clozapine Comparator	No. of Patients	SMD (95% CI)
Chlorpromazine		
Hong et al. [57] 1997	40	- 0.44 (-1.07 to 0.19)
Honigfeld et al. [53] 1984	125	- 0.64 (-1.00 to -0.28)
Kane et al. [5,6] 1988	265	- 0.88 (-1.13 to -0.63)
Total	430	- 0.75 (-0.97 to -0.53)
$t^2 = 0.01$; $X_2 = 2.27$; $P = .32$; $I^2 = 12\%$		
Haloperidol		
Buchanan et al. [7] 1998	75	- 0.14 (-0.59 to 0.31)
Kane et al. [58] 2001	34	- 0.26 (-0.98 to 0.46)
Rosenheck et al. [8] 1997	423	- 0.23 (-0.42 to -0.04)
Volavka et al. [59] 2002	77	0.13 (-0.31 to 0.57)
Total	609	- 0.17 (-0.33 to -0.01)
$t^2 = 0.00$; $X_2 = 2.19$; $P = .53$; $I^2 = 0\%$		
Olanzapine		
Bitter et al. [60] 2004	140	- 0.01 (-0.34 to 0.32)
Conley et al. [61] 2003	13	- 0.55 (-1.69 to 0.59)
Meltzer et al. [62] 2008	40	0.03 (-0.59 to 0.65)
Moresco et al. [63] 2004	15	- 0.43 (-1.48 to 0.62)
Naber et al. [64] 2005	108	0.08 (-0.30 to 0.46)
Tollefson et al. [65] 2001	176	0.14 (-0.16 to 0.44)
Volavka et al. [59] 2002	79	0.47 (0.02 to 0.92)
Total	571	0.10 (-0.07 to 0.27)
$t^2 = 0.00$; $X_2 = 5.36$; $P = .50$; $I^2 = 0\%$		
Risperidone		
Azorin et al. [56] 2001	256	- 0.33(-0.58 to -0.08)
Bondolfi et al. [66] 1998	86	0.18 (-0.25 to 0.61)
Breler et al. [67] 1999	29	- 0.44 (-1.18 to 0.30)
McGurk et al. [68] 2005	52	0.03 (-0.52 to 0.58)
Volavka et al. [59] 2002	81	0.25 (-0.18 to 0.68)
Wahlbeck et al. [69] 2000	19	0.63 (-0.29 to 1.55)
Total	523	0.00 (-0.29 to 0.29)
$t^2 = 0.07$; $X_2 = 10.92$; $P = .05$; $I^2 = 54\%$		
Ziprasidone		
Sacchetti et al. [70] 2009	144	0.02 (-0.31 to 0.35)
Total	144	0.02 (-0.31 to 0.35)
$t^2 = 0.09$; $X_2 = 67.75$; $P < .001$; $I^2 = 70\%$		
Combined	2277	- 0.11 (-0.28 to 0.06)

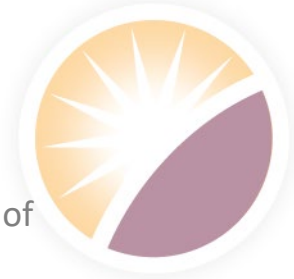


- 40 RCTs (n=40) in TRS; total n=5172
- Efficacy rankings:
  - Olanzapine > Quetiapine, Haloperidol, Sertindole
  - Clozapine > Haloperidol, Sertindole
  - Risperidone > Sertindole
- Insufficient evidence to support superiority of Clozapine to other second generation APs

Samara MT, et al. *JAMA Psychiatry*. 2016;73(3):199-210.

Other Results

- Recent meta-analysis showing CLZ superiority over other antipsychotics (Leucht et al, Lancet 2013)
- Non randomized observations favoring Clozapine (Agid et al, 2013)
- Clozapine and LAIs were the medications with the highest rates of relapse prevention in schizophrenia (Tihonen et. al, 2017)
- 2017 Canadian Schizophrenia Guidelines:
  - Clozapine should be offered to patients who have TRS
  - Clozapine should be considered for patients whose schizophrenia has not responded to two antipsychotics



Tihonen J, et. al. Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29,823 Patients With Schizophrenia. Jama Psychiatry. 2017 Jul 1;74(7):686-693.

Possible Methodological Explanation

Kane and Correll, 2016:

- Increasing placebo effect over last decades
- Variations in definitions of treatment-refractoriness
- Variations in documenting prospective trials before inclusion in studies
- Insufficient Clozapine dose
- Possible unblinding (e.g., differences in side-effects profiles)

Possible Methodological Explanation

- Other results:
  - Recent meta-analysis showing CLZ superiority over other antipsychotics (Leucht et al, Lancet 2013)
  - Non randomized observations favoring Clozapine (e.g., Agid et al, 2013)

"…our first reaction is how unfortunate it is that our field still struggles with this question more than 25 years after the 1988 publication by Kane et al led to the introduction of clozapine into clinical care in the United States…"

- Probably premature to change Clozapine guidelines at this stage

What do the Guidelines say?

- As of today, the superior efficacy of Clozapine in TRS is still recognized

- Major guidelines all state that two adequate trials that do not lead to a satisfactory response would warrant a Clozapine trial

NICE guideline. http://www.nice.org.uk/. Published 2009. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines. (2005) *Aust N Z J Psychiatry* 39(1-2):1-30. Kreyenbuhl J, et al; Schizophrenia Patient Outcomes Research Team (PORT). (2010) *Schizophr Bull.* 36(1): 94-103. American Psychiatric Association. *Am J Psychiatry,* 2004; 161:1-56. Clinical practice guidelines. *Can J Psychiatry*. 2005;50(13) Suppl 1:7S-57S.

What do the Guidelines say? *(continued)*

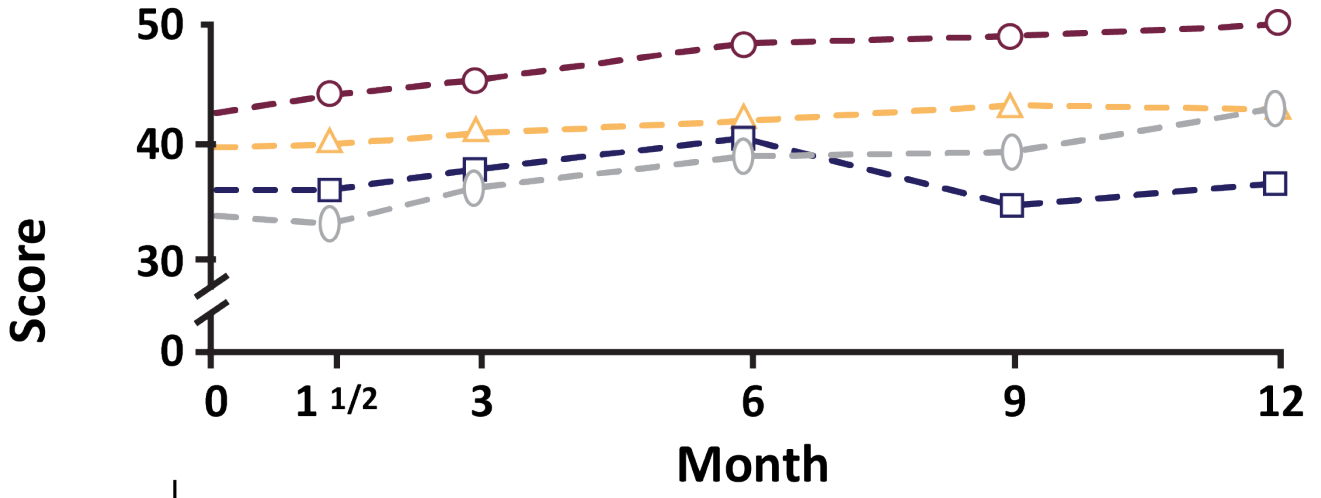
- Definition of an adequate trial may differ:
  - Lower dosage in younger and older patients?
  - Shorter duration in the absence of an early response?
  - Longer duration for a long-acting injectable antipsychotic (LAI) trial?

- Some mention considering, among these two trials:
  - One with LAI, to ensure adherence
  - One with Olanzapine, given signals for a better efficacy

NICE guideline. http://www.nice.org.uk/. Published 2009. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines. (2005) *Aust N Z J Psychiatry* 39(1-2):1-30. Kreyenbuhl J, et al; Schizophrenia Patient Outcomes Research Team (PORT). (2010) *Schizophr Bull.* 36(1): 94-103. American Psychiatric Association. *Am J Psychiatry,* 2004; 161:1-56. Clinical practice guidelines. *Can J Psychiatry*. 2005;50(13) Suppl 1:7S-57S.

Does This Better Efficacy Translate Into Better Functioning?

Quality-of-Life Outcomes (Total Scores on the Heinrichs–Carpenter Scale) among Patients Assigned to Clozapine or Haloperidol, According to Whether They Completed Treatment or Crossed Over to the Other Treatment



(p = 0.003)

Number of patients evaluated at each follow-up						
○ Completed clozapine	122	119	119	121	121	121
△ Completed haloperidol	169	152	144	130	112	111
□ Crossed over to haloperidol	83	65	54	48	43	41
⬯ Crossed over to clozapine	49	46	46	46	46	46

Rosenheck R, et al. *NEJM*. 1997;337(12):809-815.

Positive Outcomes with Clozapine

Positive Outcomes Include:
Superior efficacy for positive symptoms
Possible advantages for negative symptoms
Virtually no EPS or TD[1]
Advantages in reducing hostility/violence[2]
Suicide prevention in high risk schizophrenia and schizoaffective patients[3]
May reduce substance abuse (alcohol and cannabis)[4,5]
Lower mortality rate compared to other antipsychotics[6,7]
Fewer days of hospitalization[8]
Adherence to treatment[9]

1. Hazari N, et al. *Asian J Psychiatr* 2013,6(6):439-51. 2. Frogley A, et al. *Int J Neuropsychopharmacol;* 2012, 15(9):1351–1371. 3. Meltzer HY, et al *Arch Gen Psychiatry*; 2003, 60(1):82-91. 4. Brunette MF, et al. *J Dual Diagn* 2011;7(1-2): 50–63. 5. Zhornitsky S, et al. *J Clin Psychopharmacol* 2010;30:417-424. 6. Tiihonen J, et al. *Lancet;* 2009,374(9690):620-7 7. De Hert M, et al. *Schizophr Res* 2010;117:68-74. 8. Nielsen J, et al. J *Clin Psychopharmacol* 2012;32:678-683 9. Moisan J, et al. *Clinical Therapeutics.* 2010;32:S21-S31.

Positive Outcomes with Clozapine

Positive Outcomes Include:
Superior efficacy for positive symptoms
Possible advantages for negative symptoms
V
A
S
M
Lower mortality rate compared to other antipsychotics[6,7]
Fewer days of hospitalization[8]
Adherence to treatment[9]

These outcomes are particularly relevant for early intervention!

1. Hazari N, et al. *Asian J Psychiatr* 2013,6(6):439-51. 2. Frogley A, et al. *Int J Neuropsychopharmacol;* 2012, 15(9):1351–1371. 3. Meltzer HY, et al *Arch Gen Psychiatry*; 2003, 60(1):82-91. 4. Brunette MF, et al. *J Dual Diagn* 2011;7(1-2): 50–63. 5. Zhornitsky S, et al. *J Clin Psychopharmacol* 2010;30:417-424. 6. Tiihonen J, et al. *Lancet;* 2009,374(9690):620-7 7. De Hert M, et al. *Schizophr Res* 2010;117:68-74. 8. Nielsen J, et al. J *Clin Psychopharmacol* 2012;32:678-683 9. Moisan J, et al. *Clinical Therapeutics.* 2010;32:S21-S31.

CLOZAPINE USE EARLY IN THERAPY

Is Clozapine Underutilized?

- Horvitz-Lennon et al, 2009
  - Underuse of Clozapine: one of the most conspicuous examples of a lack of attention to evidence-based medicine
- Variations in use:
  - New Zealand:
    - Outpatients with schizophrenia: 917/2796 (32.8%) are on Clozapine
    - 18% of EPI patients were started in two years or less from first initiation of antipsychotic and 19% in years 3-5
  - Canada: very low rate of Clozapine use!
    - < 7% of patients with schizophrenia are on Clozapine

Agid O, et al, *J Clin Psychiatry* 2001;72(11):1439-44. Horvitz-Lennon M, et al. *Health AFF* 2009;28(3): 701-12. Latimer E, et al. *Clin Schizophr Relat Psychoses 2003;*7(1):33-41. Wheeler AJ. *Ann Pharmacother* 2008;42:852-60. Williams R, et al. *CJP*. May 2016.

Clozapine Use in FEP (Agid et al, 2011)

- 244/327 FEP patients treated with risperidone/olanzapine showed a good response
  - Non-responders (20%) were offered Clozapine
  - 75% who accepted responded
  - Compared to 0% who remained on the previous antipsychotic medication

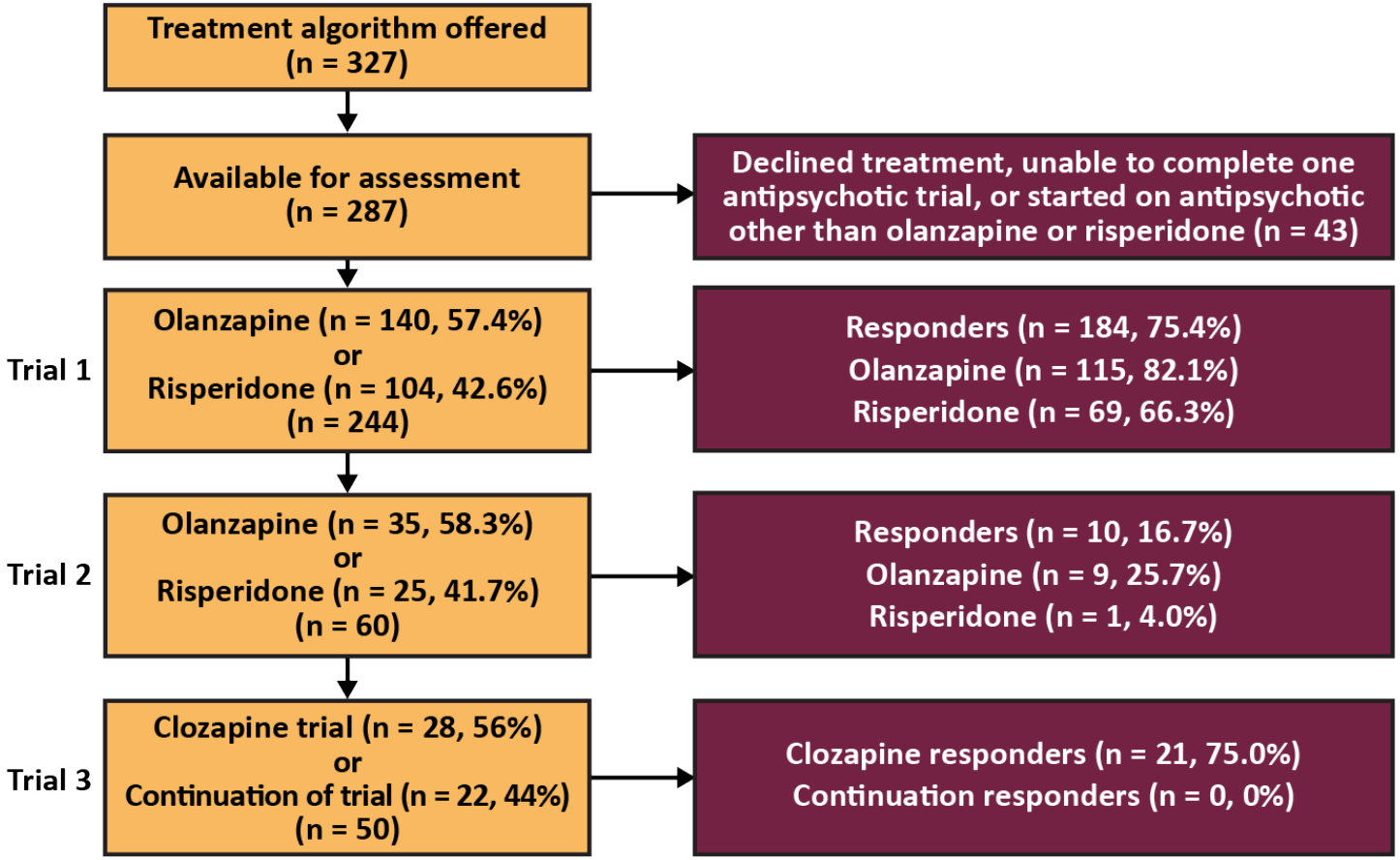
While there is a high response rate to the first antipsychotic, the rate markedly drops off among patients who require a second trial and appears to decrease even further with subsequent trials, except with Clozapine

Agid O, et al. *J Clin Psychiatry*. 2011,72(11):1439-44.

Does This Translate in Early Intervention?

An Algorithm-Based Approach to First-Episode Schizophrenia

Outcome for Treatment Algorithm in Patients (n=327)
With DSM-IV First-Episode Schizophrenia or Schizoaffective Disorder



Abbreviation: *DSM-IV* = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

Agid et al, *J Clin Psychiatry*. 2011;72(11):1439–1444

Should we use Clozapine as a First-line Treatment?

- A few RCTs have compared Clozapine to other drugs in drug-naïve FEP patients
- Thus far, no striking evidence for Clozapine superiority in this population
- No guideline currently recommends Clozapine in drug-naïve patients

Remington G, et al. *AJP*. 2013;170(2):146-151.

CCEIP National Survey: Clozapine Use

- Survey of 11 programs from Canadian Consortium for Early Intervention in Psychosis (CCEIP)
- Total number of patients = 1771,
  range per program from 45 to 392
- Various settings (academic vs. non-academic, from large metropolitan areas
  to rural settings)

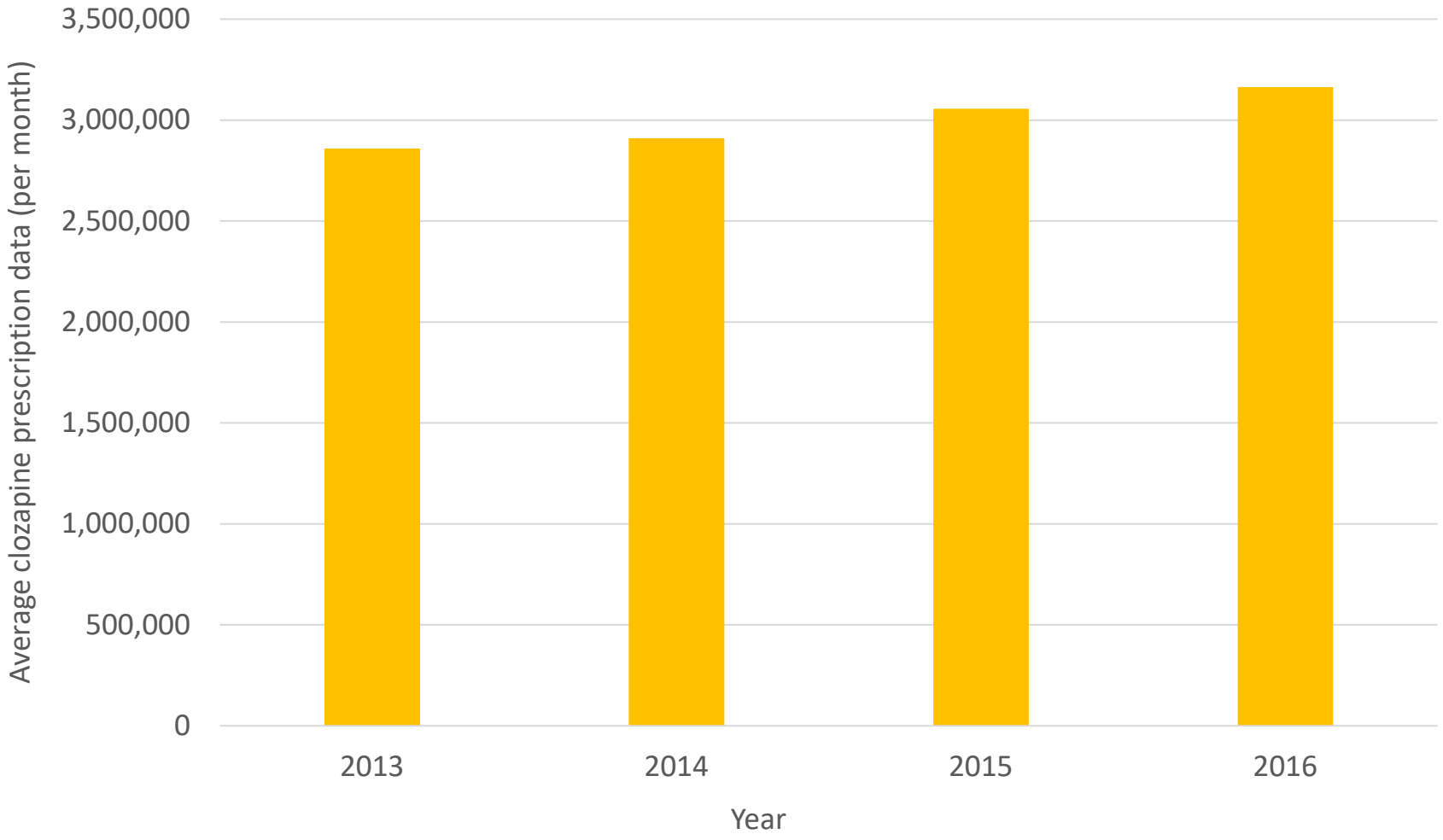
CCEIP National Survey: Clozapine Use *(continued)*

- Mean rate of use = 13.5%
- 95% Confidence of the mean = 7.1%, 19%
- Highly significant heterogeneity ($X^2 : p < 0.0001$)

CCEIP National Survey: Clozapine Use *(continued)*

- Further investigation of the sources of heterogeneity revealed more frequent use in programs:
  - Using a systematic algorithm to assess treatment resistance (17.2% vs. 10.6%)
  - With dedicated hospital beds (18.0% vs. 9.5%)
  - With a program follow up longer than two years (14.8% vs. 6.2%)

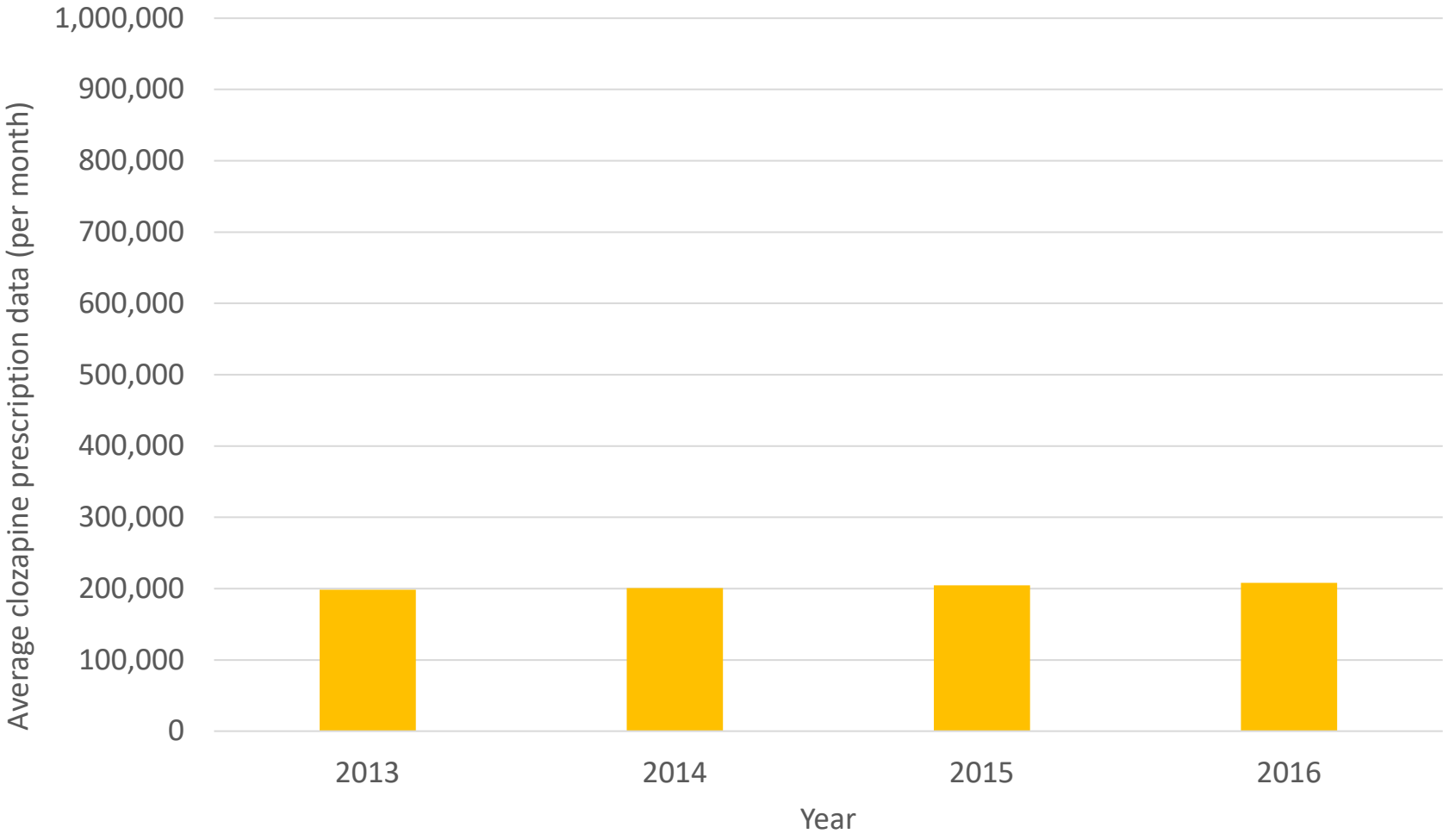
QuintilesIMS Data (2013 – 2016): *National*



QuintilesIMS/Brogran Data

(n = 119,618,400)

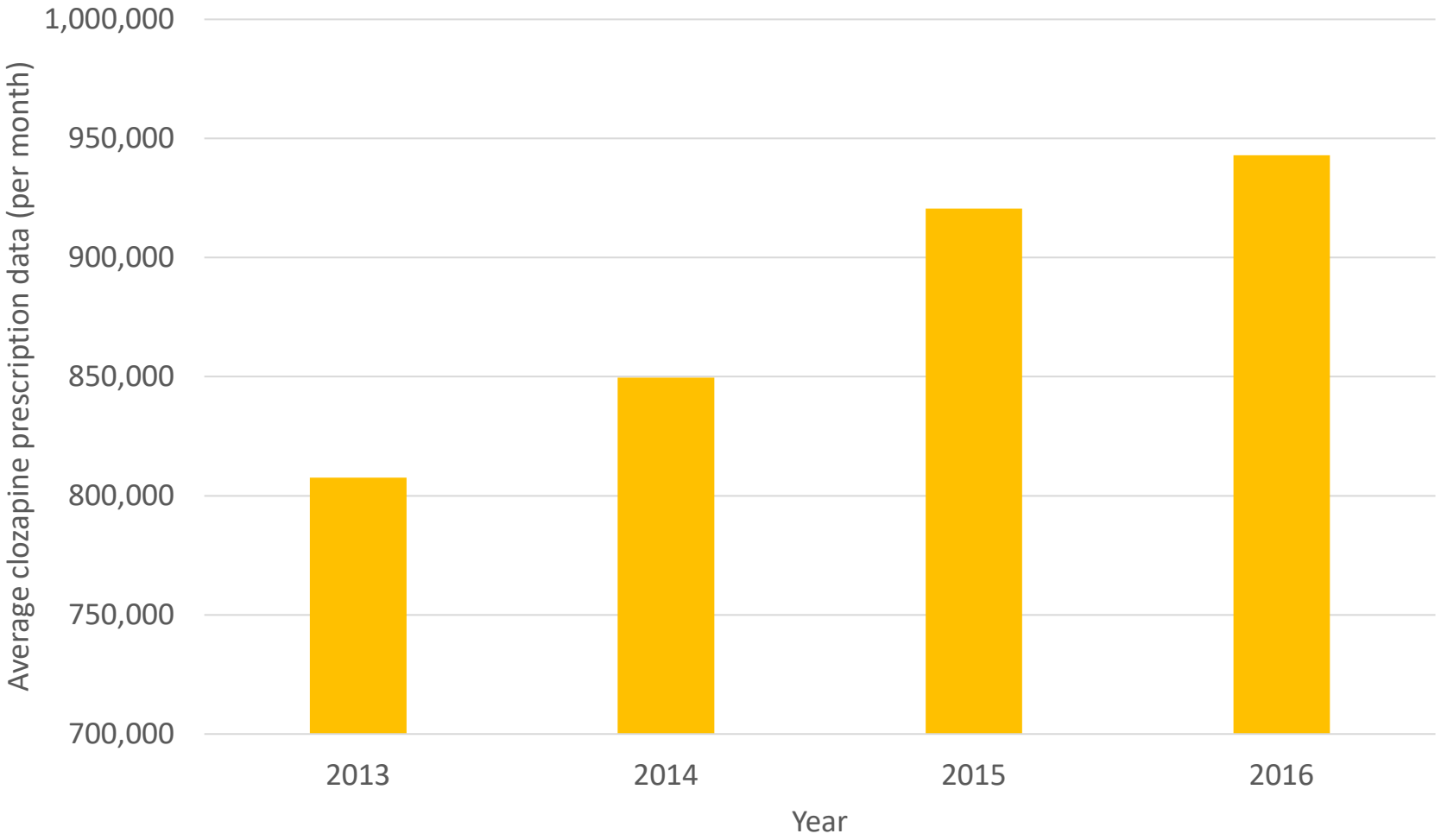
QuintilesIMS Data (2013 – 2016): *East*



QuintilesIMS/Brogran Data as of Dec 2016

(n = 8,263,900)

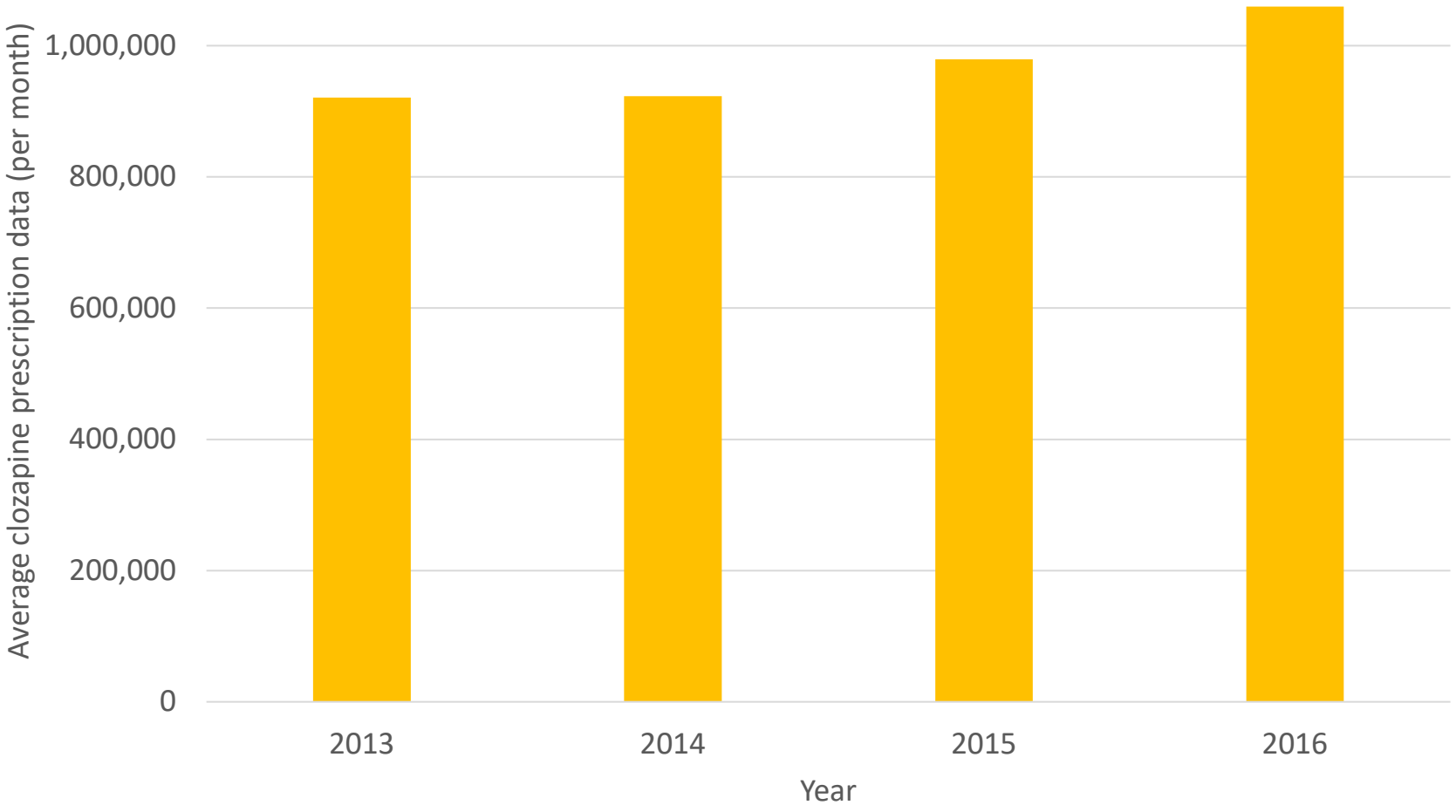
QuintilesIMS Data (2013 – 2016): *Quebec*



QuintilesIMS/Brogran Data as of Dec 2016

(n = 35,456,400)

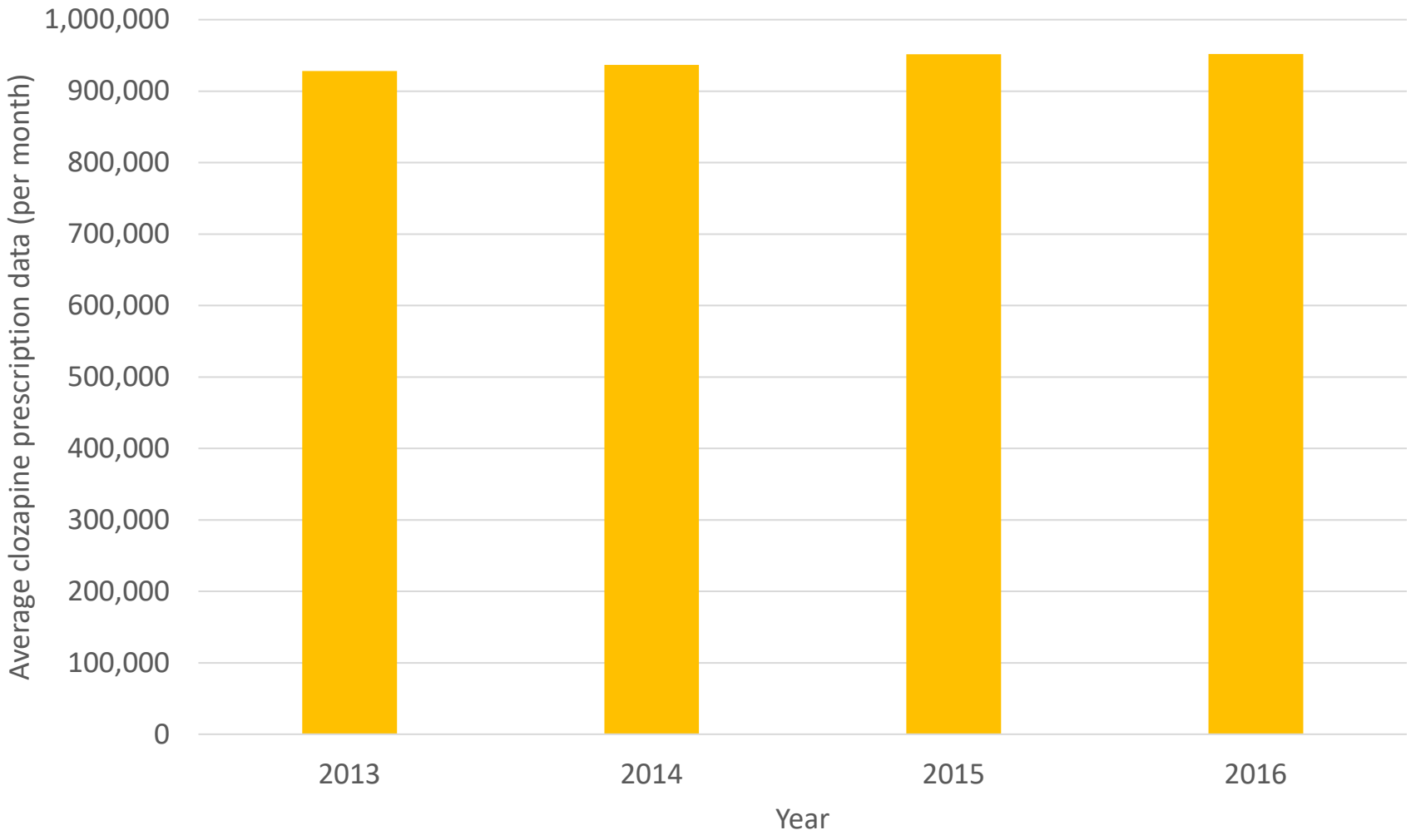
QuintilesIMS Data (2013 – 2016): *Ontario*



QuintilesIMS/Brogran Data as of Dec 2016

(n = 37,534,200)

QuintilesIMS Data (2013 – 2016): *West*



QuintilesIMS/Brogran Data as of Dec 2016

(n = 38,363,900)

Retrospective Chart Audit on Use of Clozapine: *Inclusion/ Exclusion Criteria*

- CCEIP recently completed a retrospective chart audit on use of clozapine
- Three participating centres: Dalhousie, Laval, University of Victoria
- Patients consecutively admitted to either program followed for ≥ 3 years (n = 147)
- Aged between 18-30 years old at some time during this three year follow-up
- DSM-5 diagnosis of:
  - Schizophrenia (n = 96)
  - Schizoaffective disorder (n = 18)
  - Schizophreniform disorder (n= 3)
  - Delusional disorder (n= 6)
  - Psychosis NS (n= 24)
- Patients with mood-disorders, drug-induced psychotic disorder or psychotic disorder due to a medical condition were excluded

Retrospective Chart Audit on Use of Clozapine: *Methods and Demographics*

- For each antipsychotic trial:
  - Dosage, duration and adherence were recorded
  - CGI-S once the medication was clinically judged as optimal was rated
  - Patients were considered:
    - Fully remitted when CGI-S ≤ 3 (mild, borderline or normal)
    - Partially remitted when CGI-S = 4 (moderate)
    - Not remitted when CGI ≥ 5

Population (n=147)			
Gender	118 males, 29 females		Range
Mean age at program inclusion	21.7 (sd 3.2)	3.2 (sd)	17-30
Mean age at chart review	26.5 (sd 3.9)	3.9 (sd)	21-36
Age at program inclusion	21.7 (sd 3.2)	3.2 (sd)	17-30

Retrospective Chart Audit on Use of Clozapine: *Comorbidities*

Psychiatric	
Substance use disorder	100 (68%)
Anxiety disorder	46 (31%)
OCD	6 (4%)
Major depressive disorder	23 (16%)
Post traumatic stress disorder	6 (4%)
Personality disorder	13 (9%)
ADHD	22 (15%)
Others	8 (5%)
None	22 (15%)

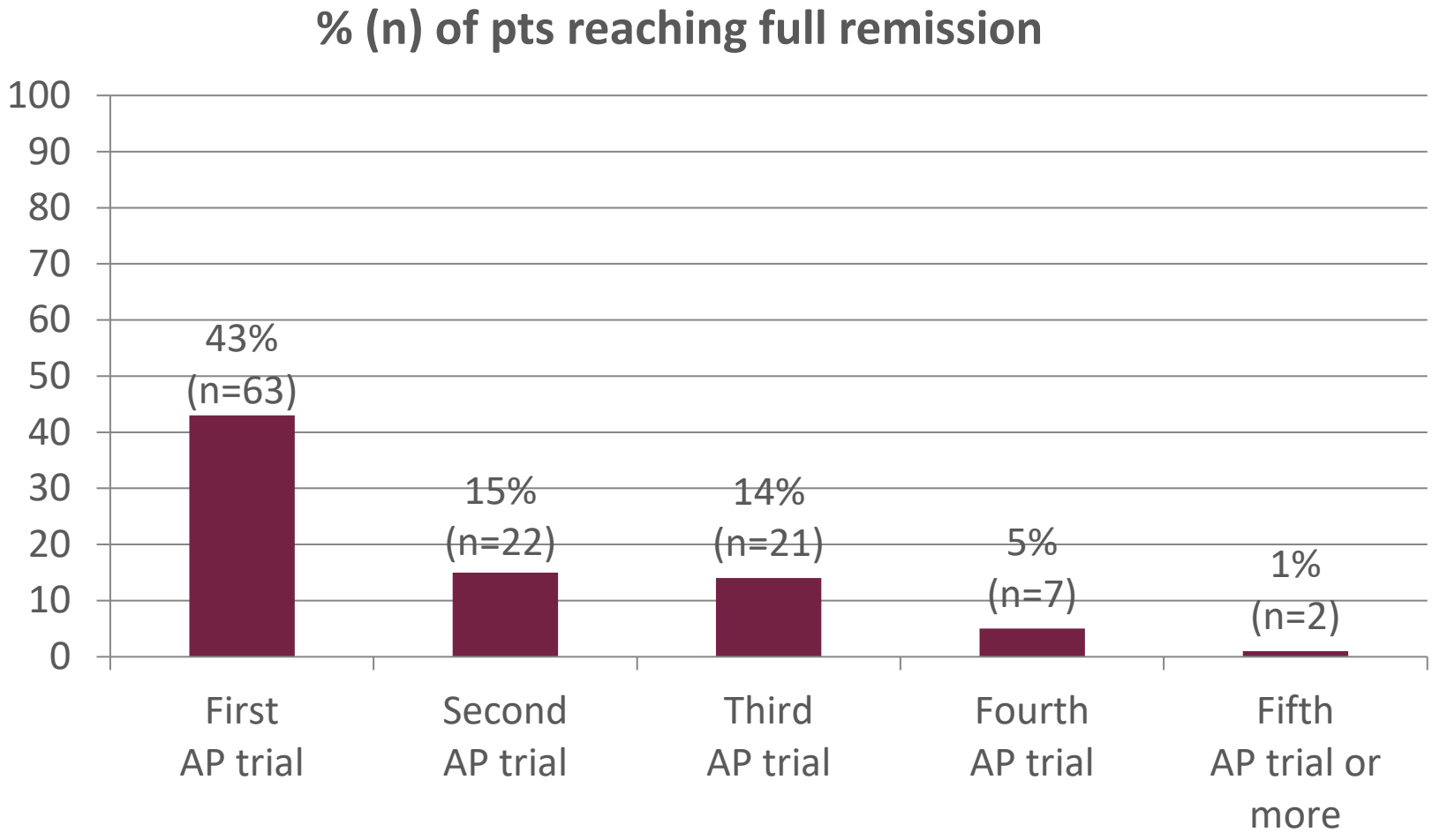
Physical	
Diabetes	1 (0.7%)
Dyslipidemia	16 (11%)
Hypertension	7 (5%)
Obesity	6 (4%)
Hypothyroidism	5 (3%)
Hyperprolactinemia	3(2%)
Others	22 (15%)
None	93 (63%)

Retrospective Chart Audit on Use of Clozapine: *Response to Treatment*

- 115/147 patients (78%) had reached full remission during the chart review interval
- More than half of them (63/115; 54%) in the first AP trial
- At the end of the chart review interval, 110/147 (75%) patients were still in full remission

Retrospective Chart Audit on Use of Clozapine:

Proportion of Patients Reaching Full Remission by Antipsychotic Trial Rank



Retrospective Chart Audit on Use of Clozapine: *Medication Pattern of Use*

Trial 1:

Risperidone (43%) > Olanzapine (21%) > Quetiapine (19%) > others
Use of LAIs (9%)
No clozapine

Trial 2:

Paliperidone (25%) > Aripiprazole (23%) > Quetiapine (19%) > others
Use of LAIs (12%)
No clozapine

Trial 3:

Clozapine (32%) > Aripiprazole (29%) > Paliperidone (14%) > others
Use of LAIs (9%)

Retrospective Chart Audit on Use of Clozapine: *Medication Pattern of Use (con't)*

LAIs

- Globally, 59/147 (40%) patients were exposed to LAIs

Clozapine

- Globally, 29/147 (20%) patients were exposed to clozapine after a mean of 2.89 AP trials

Retrospective Chart Audit on Use of Clozapine:

Patients Not in Full Remission Who Were Not Prescribed Clozapine

Reasons why Clozapine was not introduced (more than one reason can applied)	N*	%
Option never considered	5	20%
Major medical contraindication	--	--
Residual symptoms considered non-severe	5	20%
Major medication adherence problems anticipated	8	32%
Patient refusal	1	4%
Organisation of care incompatible with clozapine follow-up	--	--
Major substance use disorder	6	24%
Others	2	8%
Missing reasons	1	4%

(n = 28)

Retrospective Chart Audit on Use of Clozapine: *Reasons Why Clozapine Was Offered*

Reason	Number (%)
Insufficient response to previous trials	28 (96.6)
EPS with previous drugs	6 (20.7)
Severe impulsivity	2 (6.9)
Substance use disorder	9
Suicide risk	4
Violence	4

- Total remission was reached on clozapine for 20/29 (69%) patients
- Partial remission was reached in 9/29 (31%) of exposed patients

Retrospective Chart Audit on Use of Clozapine: *Clozapine Pattern of Use*

- Clozapine was initiated on an outpatient setting in 55% of cases
- 8/29 were previously treated with a LAI
- In the clozapine exposed group, in comparison to the others:
  - More patients were on CTO or extended leave (41 vs 28%, respectively),
  - More patients had a comorbid substance use disorder(83 vs 64%), and,
  - More personality disorder (21 vs 6%, respectively)

Retrospective Chart Audit on Use of Clozapine: *Clozapine Pattern of Use (con't)*

- Dose range from 150 to 600 mg daily,
  - Modal dose 400 mg
- Once daily regimen was used in 2/3 of cases
- Blood levels were used in 26/29 (90%) of patients

Retrospective Chart Audit on Use of Clozapine: *Limitations*

- Modest sample size
- Retrospective ratings
- Under-reporting of comorbidities

Retrospective Chart Audit on Use of Clozapine: *Conclusions*

- Clozapine is more widely used in early intervention programs than would be typically assumed
- Clozapine may be introduced in an outpatient setting
- It can be, in some instances, successfully used patients with a typical non-adherent profile
- Rates of response may be particularly high in this population

CLOZAPINE USE IN PRACTICE

What are Appropriate Dosages? Product Monograph

- Available in 25, 50, 100 and 200 mg tablets and 50 mg/ml oral suspension
- Therapeutic Dose Range:
  - 300-600 mg/day in divided doses (may be divided unevenly, with the larger portion at bedtime)
  - May require higher doses (600-900 mg/day), but increased risk for seizures
  - Lower dose(<300mg/day) may be required for FEP

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON.
Remington G, et al. *Psychopharmacology*. 2013;225(3):505-518.

How Should Clozapine be Initiated?

- RCT: mostly used bid dosage
- AM dose = causes drowsiness/sedation
- Single hs dose most frequently used
  - 75% of cases took the dose at bedtime
- Gradual titration
  - Increase dose by 6.25-12.5 mg/day until response
  - Gradual decrease of previous drug, according to the dosage, response and side-effects that may limit Clozapine up titration

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON,
Remington G, et al. Psychopharmacology. 2013;225(3):505-518.

How Should Clozapine be Initiated? *(continued)*

- Can be initiated on an outpatient basis with proper support and if patient's clinical status allows
  - Less rapid increase if initiated as outpatients

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON,
Remington G, et al. Psychopharmacology. 2013;225(3):505-518.

Role of Blood Levels

- In general, blood levels correlate better than actual dosage to clinical response and side effects
- Optimal dosage may require levels ≥ 1500 nmol/L
- Response may be obtained with lower blood levels
- Important variability in metabolism → broad inter-individual variations in levels with a given dosage
- Blood levels may be helpful to:
  - Monitor interactions
  - Assess adherence to treatment
- Nor-Clozapine levels and Clozapine/Norclozapine ratio: unknown significance

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON.
Remington G, et al. Psychopharmacology. 2013;225(3):505-518.

Drug Pharmacodynamic Interactions

- May enhance the sedative effects of other drugs:
  - Beware, in particular, of i.m. Lorazepam
- Beware of drugs that can suppress bone marrow function:
  - Carbamazepine is to be avoided
  - Other drugs may contribute to a lesser extent:
    - Valproate, Quetiapine

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON.

Drug Pharmacodynamic Interactions *(continued)*

- Be cautious about anti-cholinergic effects (memory, constipation, etc.)
    - Benztropine, paroxetine, etc.

- Monitor ECG if combined with drugs known to increase the QTc interval, e.g.:
    - Other antipsychotics
    - Antidepressants
    - Lithium
    - Pantoprazole, domperidone
    - Some antibiotics (clarithromycin, quinolones)

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON.

Drug Pharmacokinetic Interactions

- Oxydative hepatic metabolism (CYP450)
  - Main pathway: CYP450 1A2
  - Other: 2D6, 3A4
  - **Monitoring through blood levels**

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON.

Other Drugs Known To Inhibit Cytochrome P450 May *Increase* Clozapine Levels

- Fluvoxamine: 1A2 +++ (also, 2D6)
- Ciprofloxacin (Cipro) : 1A2 +++
- Clarithromycin (Biaxin) : 3A4
- Duloxetine: 1A2, 2D6
- Oral contraceptives: 1A2, 3A4, 2C19
- Fluoxetine, paroxetine: 2D6; Norfluoxetine 3A4
- Venlafaxine: 2D6
- Sertraline, citalopram (to a lesser extent): 2D6

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON.

+++ indicates interactions that are particularly potent

Concomitant Administration Of Cytochrome P450 Inducers May *Lower* Clozapine Blood Levels

- **Tobacco smoking: 1A2 (not nicotine, but smoke)**
- Omeprazole (Losec) : 1A2
- Ritonavir (for HIV): 1A2
- Anticonvulsants [Phenytoin (Dilantin), Primidone (Mysoline)]: 3A4
- Rifampicin (tuberculosis): 1A2
- Again, monitor blood levels, assess response and adjust dosage accordingly

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON.

Most Important Information for the Patient

Topics to focus on during your discussion:

- Missed doses:
  - ≥ 48 hours: gradual re-initiation
  - < 48 hours: may split doses to reach planned daily dosage
- Abrupt withdrawal may be quite unpleasant: anticholinergic rebound
- Interactions: systematically inform pharmacist and physician

Most Important Information for the Patient *(continued)*

Topics to focus on during your discussion:

- Smoking: variations may influence side-effects and efficacy
- Constipation: systematically report!
- Blood testing: do not miss!
- May take time to fully assess the results
- Response can take a while to become apparent, but increases with time
- Side effects decrease with time

Perspective on Clozapine's Side Effects

- Clozapine is not dangerous if properly used
- People on Clozapine may have a longer life expectancy than those treated on other antipsychotics/untreated
- Side effects need to be systematically assessed and diligently treated; most are easy to manage
- Generally possible to identify a well tolerated and efficacious dosage

Tiihonen J, Lönnqvist J, Wahlbeck K, et al. *The Lancet*. 2009;374(9690):620-627.

Potential Side Effects

More common

- Drowsiness/sedation
- Weight gain
- Hypersalivation
- Enuresis
- GERD (reflux)
- Constipation
- Tachycardia
- Dizziness/vertigo
- Headache
- Tremor
- Fever
- Disturbed sleep/nightmares
- Postural hypotension
- Metabolic side effects
- Increased risk of diabetes
- Obsessive compulsive symptoms

Rare but severe

- Agranulocytosis/ granulocytopenia
- Myocarditis
- Cardiomyopathy
- Pericarditis
- Seizures

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON,
Meltzer HY, et al. *Arch Gen Psychiatry*. 2003;60(1):82-91.

Managing Common Side Effects

Weight Gain

- Very broad inter-individual variability
- Psychiatric and functional improvements sometimes lead to better life hygiene
- Limited impact of drugs to limit weight gain
- Stress exercise and diet

GERD

- Relatively frequent
- Systematically assess symptoms
- Easily managed:
  - E.g., Pantoprazole 40

Greg Deardorff O, et al. *Prim Care Companion CNS Disord*. 2014;16(3), Taylor D, et al. *Journal of Clinical Psychopharmacology*. 2010;30(4):460-461.

Managing Common Side Effects

Tachycardia

- Monitor pulse/BP
- Verify whether this is reflex tachycardia associated with postural hypotension
- Adding a cardio-selective beta blocker:
  - Bisoprolol 2.5-5 mg /day
  - Metoprolol 25 mg/day with consistent tachycardia >120 bpm

Hypersalivation

- Ask the question
- Pharmacological:
  - Atropine 1% ophthalmic drops
    - Sublingual 1 drop or more on either side at bedtime
  - Cogentin/Kemadrin small doses at HS
- Non-pharmacological:
  - Use mouthwash before bed
  - Sham-wow or other absorbent towel on pillow or between pillow case and pillow to avoid towel face in am

Sagy R, Weizman A, Katz N. *International Clinical Psychopharmacology*. 2014;29(6):313-317.

Managing Common Side Effects

Enuresis

- More frequent than generally thought
- Patients often won't report due to shame
- Management:
  - Water restriction
  - Systematically go to toilet before bed
  - DDAVP may be used but risk of hyponatremia

Constipation

- Detailed questioning needed – how many times a day do you go, is it difficult, is it painful?
- Appears to be dose dependent, may lead to severe complications if left untreated
- Management:
  - Laxatives
  - Routine prophylaxis (increase activity, fibre)

Patients should undergo proper monitoring and interventions in order to minimize the burden of constipation and the risk of ileus

Sagy R, Weizman A, Katz N. *International Clinical Psychopharmacology*. 2014;29(6):313-317.
Nielsen J, Meyer JM. *Schizophr Bull*. 2012;38(3):592-598.

Side Effects: Seizures

- Clozapine lowers seizure threshold
- Seizure may occur in 3% of patients
- Risk increased with other drugs lowering seizure threshold
- This risk is dose related
- May be preceded by myoclonias: systematically assess!
- History of seizure is not a contraindication but requires special attention
- May be managed with anti-convulsants

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON.

Side Effects: Haematological

- Cumulative risk of agranulocytosis (1%)/ neutropenia (3%)
- Requires WBC count and differential count:
  - Weekly for weeks 1-26
  - Two week intervals for weeks 27-52
  - Four week intervals thereafter
- Possible use of finger-prick blood test
- Rigorous monitoring prevents most serious consequences: deaths highly uncommon
- FDA has recently released (Nov 2015) new, less stringent, WBC monitoring requirements (Canadian requirements remain the same)

Mylan Pharmaceuticals ULC (2016). Gen-Clozapine Product Monograph. Etobicoke, ON. Munro et al, *British J Psychiatry* 1999;175(6):576-580; Atkin et al, *Br J Psychiatry 1996;169(4)*483-488, FDA Drug Safety Communication. http://www.fda.gov/Drugs/DrugSafety/ucm461853.htm. Accessed June 6, 2016.

Severe Cardiac Side Effects: Myocarditis, Others

- Myocarditis is a rare, yet severe, complication
- Occurs during the first 4 to 8 weeks
- May be asymptomatic: importance of monitoring cardiac enzymes
- Cardiomyopathy and pericarditis are less frequent but may occur at times beyond the first 2 months
- Monitor QTc (refer to previous section on pharmacodynamic interactions)
- Pay attention to cardiac symptoms

Ronaldson KJ, et al. *Schizophr Res*. 2011;128(1-3):161-165, Layland JJ, et al. *Med J Aust*. 2009;190(4).

Cardiac Monitoring: UP TO DATE

- All patients should be monitored closely for at least the initial 4 weeks of treatment including:
  - Assessment of symptoms of myocarditis (e.g. malaise, chest pain, shortness of breath)
  - Vital signs at each visit
  - ECG at baseline
  - Weekly blood work including: eosinophil count, troponins, sedimentation rate (i.e. ESR) or C-reactive protein
- A significant increase in C-reactive protein (> 100 mg/L) and troponin elevation (> 2x upper normal limit) have been reported to be 100% sensitive in detecting Clozapine-induced myocarditis in symptomatic patients. Eosinophil counts are less reliable and delayed
- Echocardiogram in patients with suspected cardiomyopathy or myocarditis/pericarditis

Ronaldson KJ, et al. *Schizophr Res*. 2011;128(1-3):161-165,
Layland JJ, et al. *Med J Aust*. 2009;190(4).

WHAT IF CLOZAPINE FAILS?

Should We Be Combining Antipsychotics?

- Antipsychotic combinations are frequently used
- Few studies on this strategy
- Very scant evidence to suggest superiority to monotherapy
- Concerns about safety
- Switch studies suggest that it is possible to go back to monotherapy in most cases
- Should not be routinely used

Correll CU, et al. *Schizophr Bull*. 2009;35(2):443-457, Honer WG, et al. *New England Journal of Medicine*. 2006;354(5):472-482. Stahl SM. *Acta Psychiatrica Scandinavica*. 2012;125(5):349-351

Combining Antipsychotics

- There is no clear rationale for requiring antipsychotic combinations prior to Clozapine in TRS
- In TRS, use of Clozapine carries the best odds of obtaining a robust response
- If Clozapine does not provide robust response, combination with other APs may be considered

Correll CU, et al. *Schizophr Bull*. 2009;35(2):443-457, Honer WG, et al. *New England Journal of Medicine*. 2006;354(5):472-482. Stahl SM. *Acta Psychiatrica Scandinavica*. 2012;125(5):349-351

Combine with ECT?

Prospective Randomized Study (Petrides et al 2015)		**N = 39**	**% Responders**
Trial 1	ECT + Clozapine Clozapine	20 19	50% 0%
Trial 2	Clozapine + ECT	19	47%
Meta-analysis (Lally et al 2016)		**N =**	**% Responders**
RCTs and open label trials	ECT + Clozapine	71	54%
Retrospective chart reviews, case series and case reports	ECT + Clozapine	126	66%

Mean number of ECT treatments used to augment clozapine was 11.3. 32% of cases (20 out of 62 patients) with follow-up data (range of follow up: 3–468 weeks) relapsed following cessation of ECT. Adverse events were reported in 14% of identified cases (24 out of 166 patients).

Petrides G, et al. *Am J Psychiatry* 2015;172(1):52-8. Lally J, et al. *Schizophrenia Research* 2016;171(1):215-224.

Psychosocial Interventions

- Psychosocial approaches may decrease the severity of symptoms in psychosis, including:
  - CBT
  - Cognitive remediation
  - Employment support programs
  - Family interventions
  - Housing support
- There is evidence that combining such interventions improves Clozapine impact

Williams R, et al. *CJP*. May 2016; Rosenheck R, et al. *Arch Gen Psychiatry*. 1998;55(7):618-625.

Conclusions

- Clozapine:
  - Should be considered whenever results with 2 adequate antipsychotic trials are insufficient
  - May offer important benefits beyond superior efficacy
  - Is not a dangerous drug if properly used
  - Should not be limited to very chronic and very severe forms of psychosis