Retour de Post-doctorat 2018-2019
Travaux en Pharmaco-épidémiologie

Department of Epidemiology, Biostatistics, and Occupational Health, McGill University
Centre for Clinical Epidemiology, Lady Davis Institute, Montreal, QC, Canada

Dr François Montastruc

Présentation unité INSERM 1027

17 Janvier 2019

McGill

Plan

1. Mon parcours
2. Equipe de pharmaco-épidémiologie de McGill
3. Travaux effectués
   a. *Trends in First Gabapentin and Pregabalin Prescriptions in Primary Care in the United Kingdom, 1993-2017.*
   b. *Association of Aripiprazole With the Risk of Psychiatric Hospitalization, Self-Harm, or Suicide*
4. Collaborations
5. Conclusion

Parcours hospitalo-universitaire

- **2003-2009** : **Études médicales**, Faculté de Médecine Toulouse

- **2009-2014 : Interne des Hôpitaux de Toulouse**, Santé Publique
  - **2013 DIU « PharmacoPsychiatrie générale »,** Université Pierre et Marie Curie
  - **2014 DES Santé Publique et Médecine Sociale,** Université Paul Sabatier

- **2014 – Aout 2017 : Assistant Hospitalo-Universitaire**

  Service de Pharmacologie Médicale et Clinique de Toulouse

- **Septembre 2017 – Aout 2018 : Postdoctoral fellow**

  Centre d'Epidémiologie Clinique, McGill, Montréal

- **Depuis Septembre 2018 : Chef de clinique**

  Service de Pharmacologie Médicale et Clinique de Toulouse

Formations à la recherche

- **2011 : M1 de Santé Publique,** Université Paul Sabatier
  - "The importance of drug-drug interactions as a cause of adverse drug reactions: a pharmacovigilance study of serotoninergic reuptake inhibitors in France."

- **2013 : M2 Recherche "Santé Publique Epidémiologie", ISPED** Université Bordeaux
  - « Participation des récepteurs sérotoninergiques 5-HT2c et histaminergiques H1 dans les diabètes induits par les antipsychotiques : étude pharmaco-épidémiologique/pharmacodynamique dans VigiBase. »

- **2017 : Doctorat d'Université de Bordeaux,** INSERM U 1219, Bordeaux
  - « Neuroleptiques chez l'enfant, l'adolescent, et l'adulte jeune : évaluation pharmaco-épidémiologique de l'utilisation et des risques associés »

- **2018 : Postdoctoral fellow,** Centre d'Epidémiologie Clinique,, McGill, Montréal

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Equipe

- Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada
  - **Centre for Clinical Epidemiology, Lady Davis Institute, Jewish general hospital, Montreal, QC, Canada**
  - Direction: Dr Samy Suissa
    - 27 chercheurs principaux + 28 collaborateurs actifs

1. Epidémiologie clinique
2. **Pharmaco-épidémiologie**
3. Epidémiologie génétique

Equipe de pharmaco-épidémiologie

Dr Samy Suissa

Dr Christel Renoux

Dr Robert Platt

Dr Laurent Azoulay

Dr Kristian Filion

Dr Pierre Ernst

Clinical Practice Research Datalink

CPRD UK data for Real World evidence

30
years of electronic health record data collection

90%
of UK healthcare consultations are in primary care

Over
20M
Patient lives and
5M
Currently registered patients

Over
20
countries worldwide use CPRD data producing more than
1800
Peer-reviewed publications

Longitudinal
cradle to grave

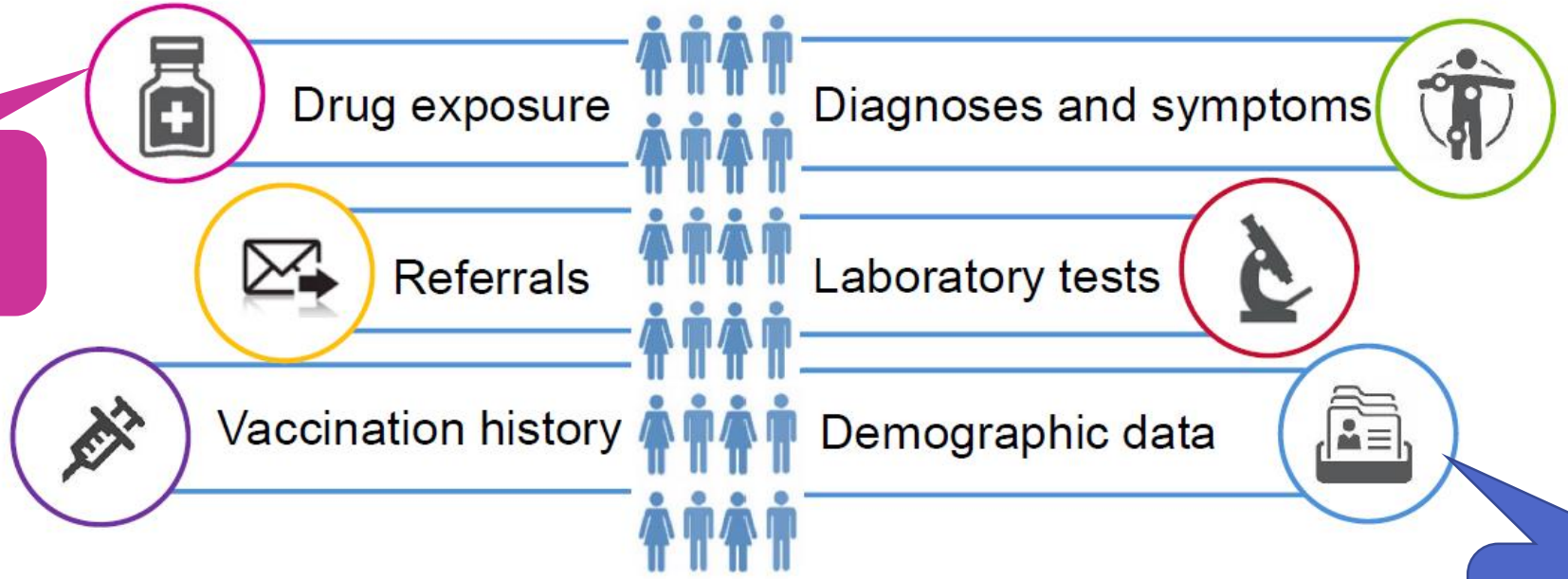
Representative
age, sex and ethnicity

Data linkage

CPRD

CPRD Data: Coded data from primary care records

1.8 billion consultations including

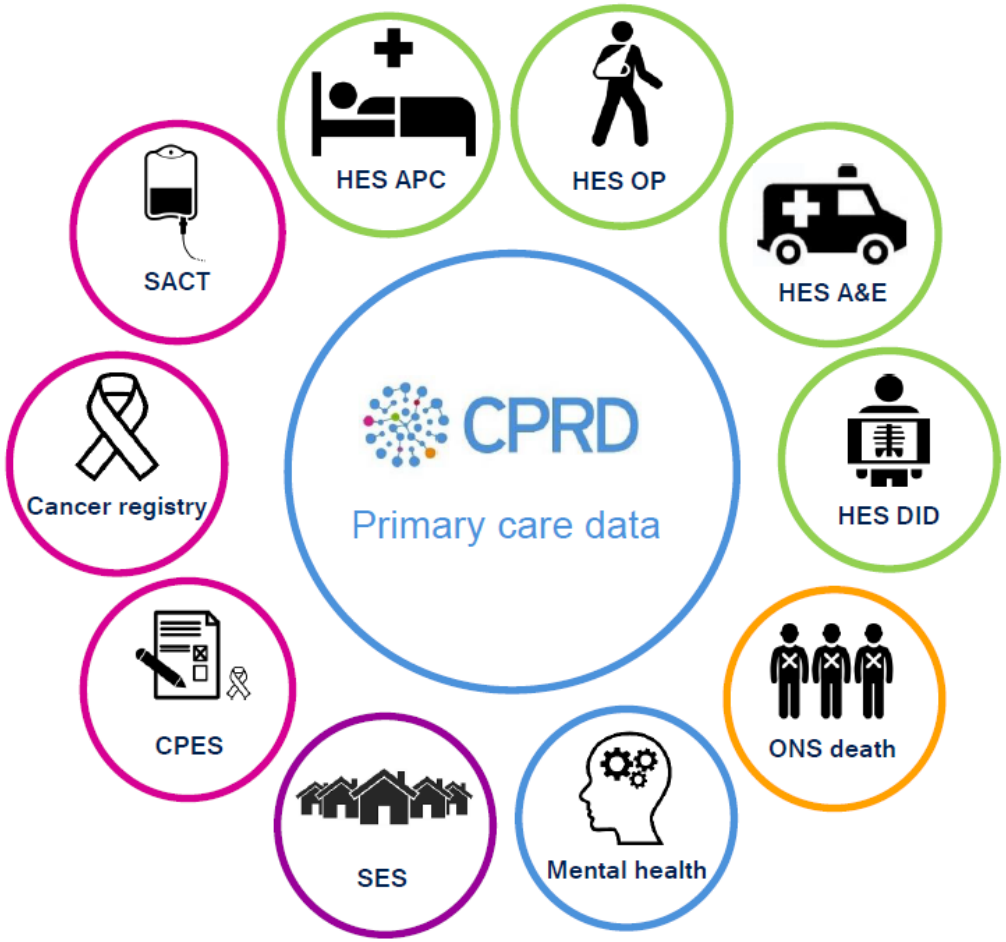


Enregistrement automatique des prescriptions

+ mode de vie (tabac, alcool..)

CPRD

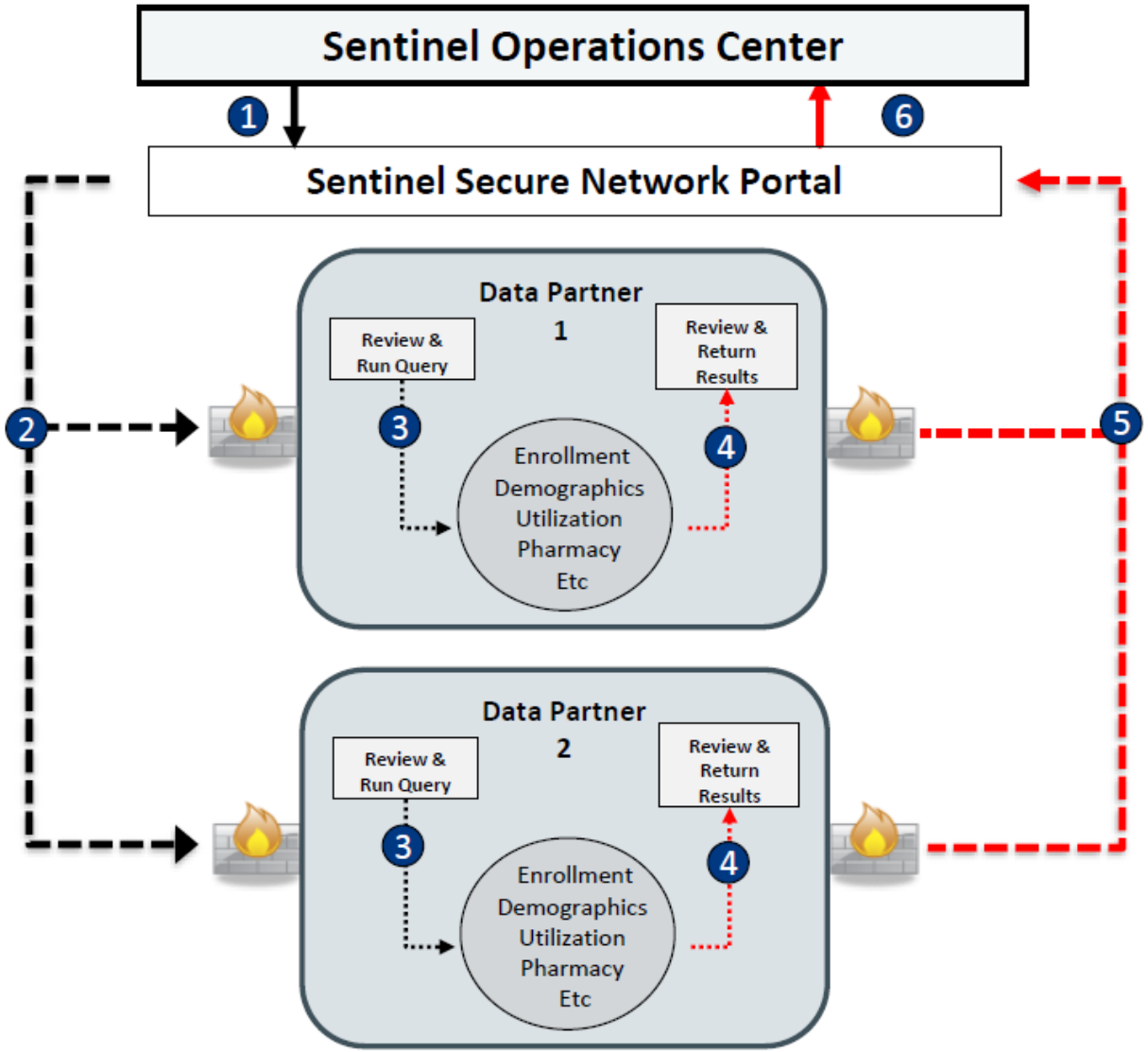
Extending scope of research through linkage



The Canadian Network for Observational Drug Effect Studies
CNODES

CNODES
CANADIAN NETWORK FOR OBSERVATIONAL DRUG EFFECT STUDIES

Sentinel distributed analysis



1- User creates and submits query

2- Data Partners retrieve query

3- Data Partners review and run query against their local data

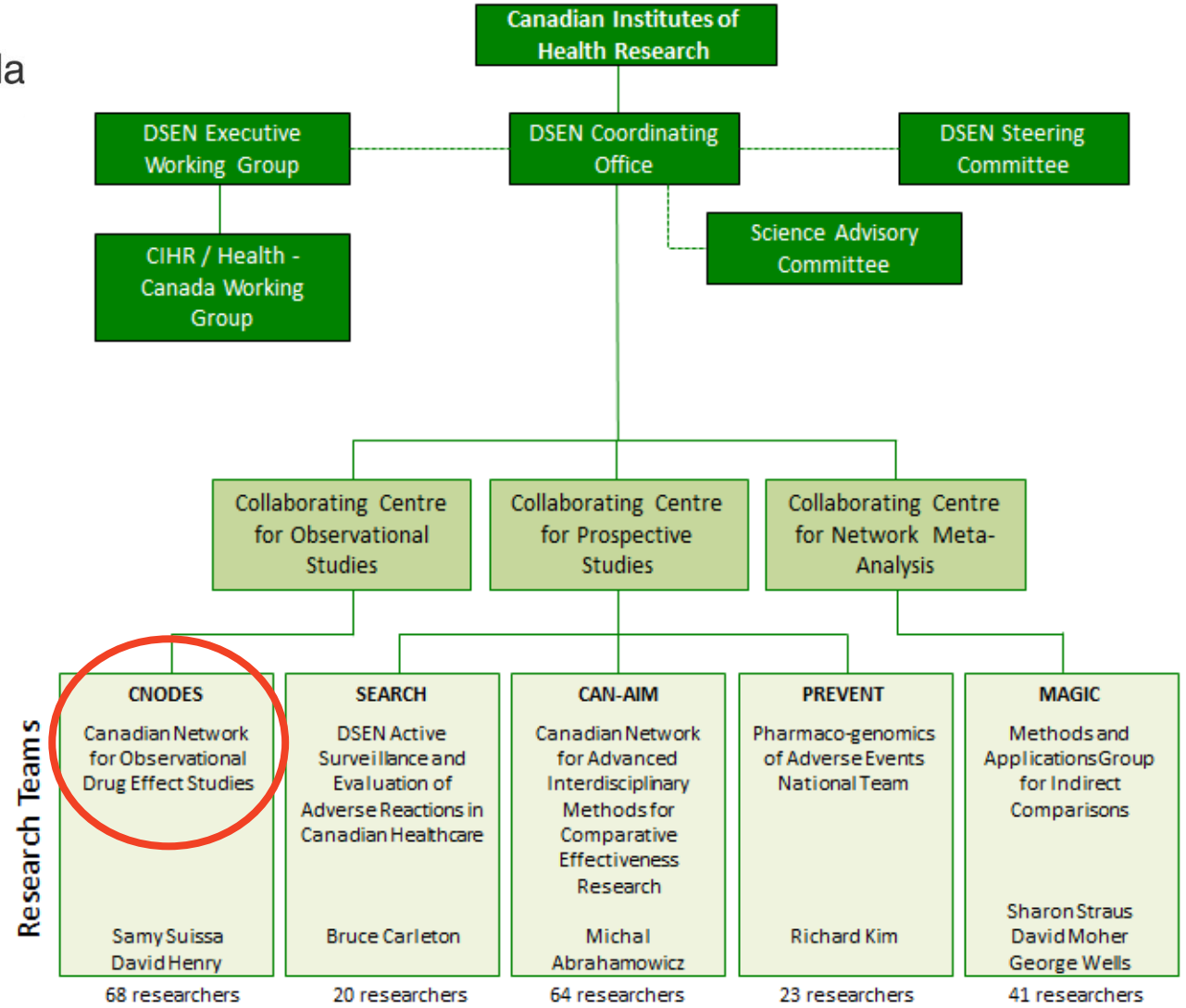
4- Data Partners review results

5- Data Partners return results via secure network

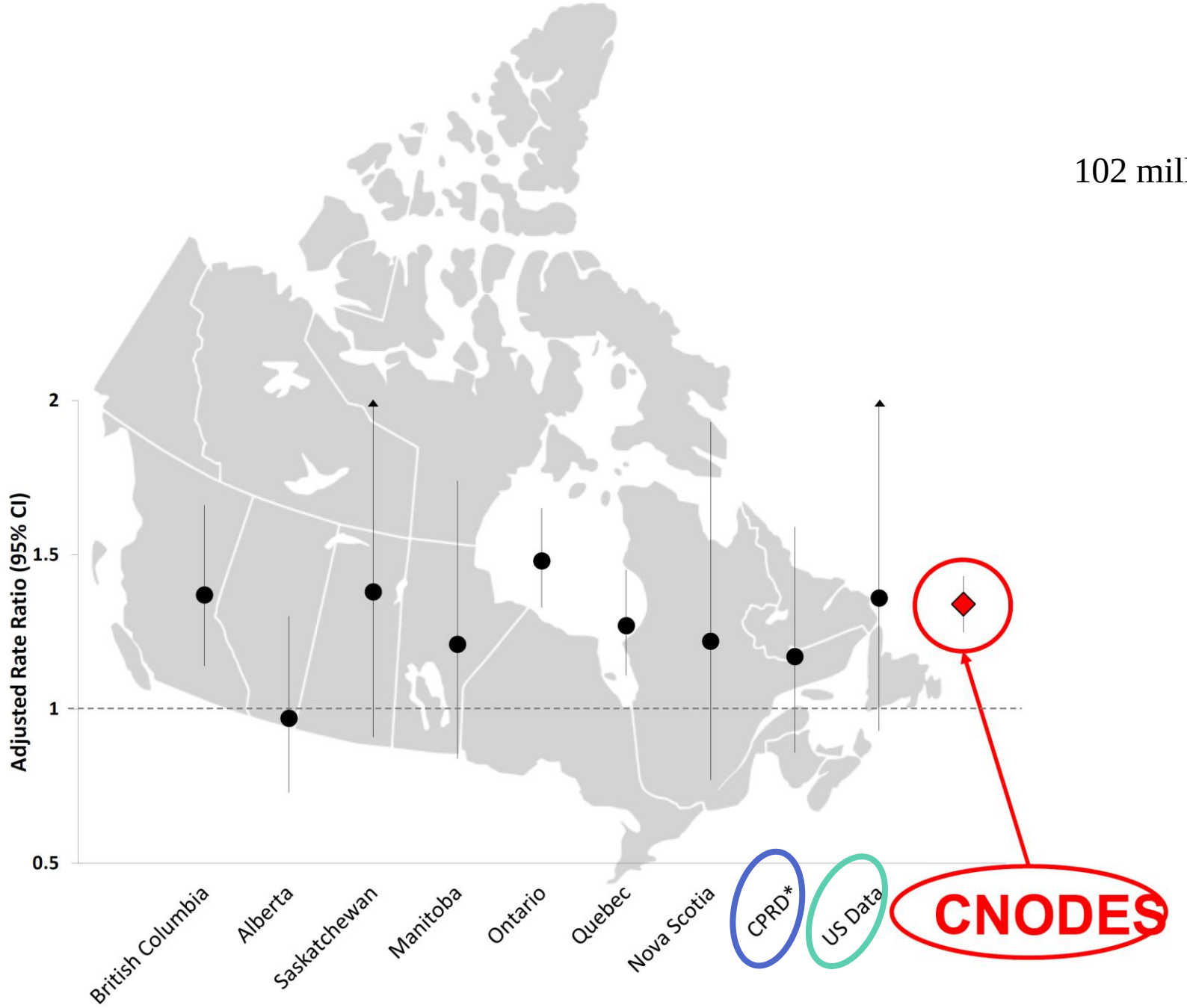
6 Results are aggregated and returned

Drug Safety and Effectiveness Network

Santé Canada Health Canada



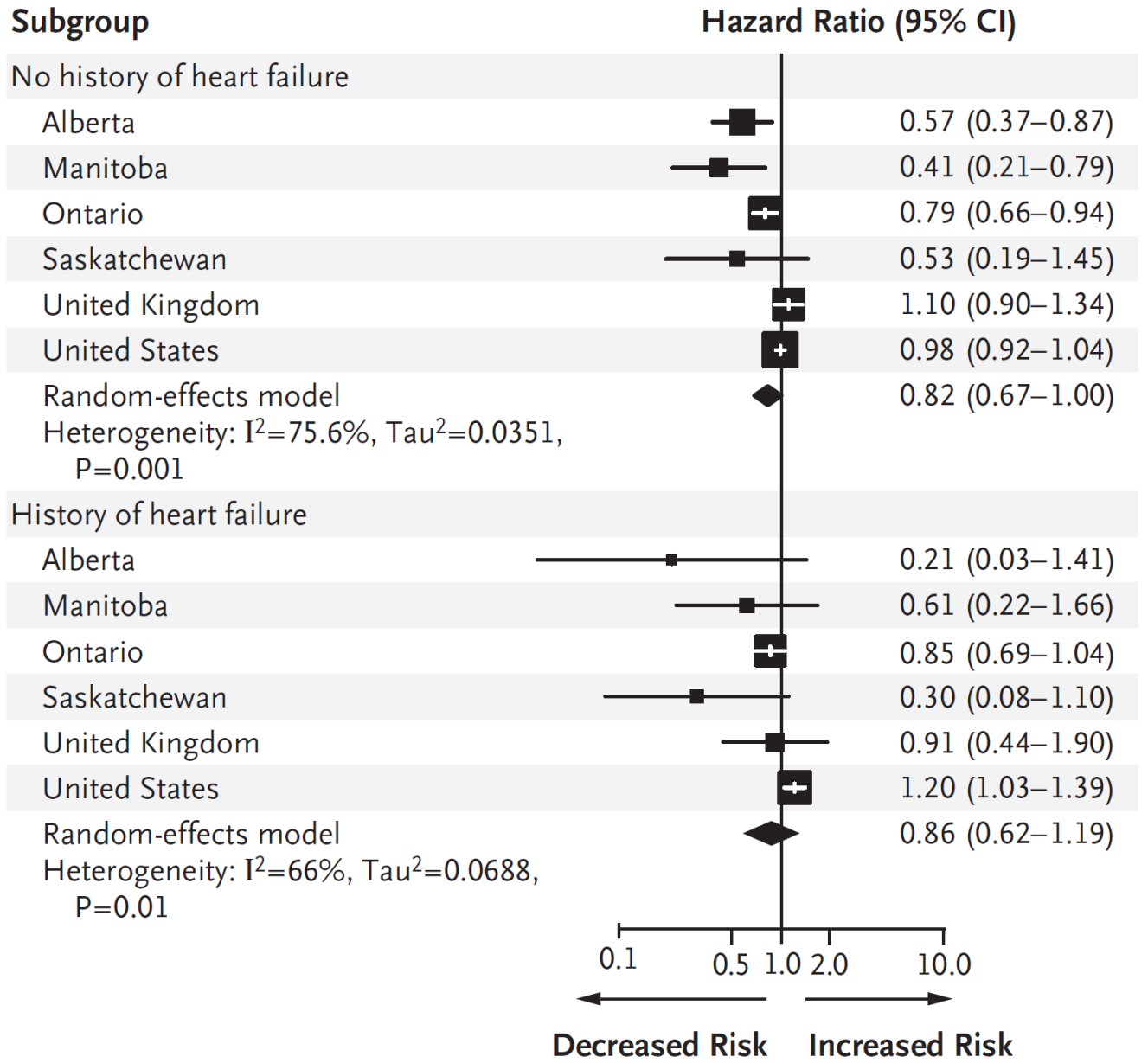
102 millions personnes



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multicenter Observational Study of Incretin-based Drugs and Heart Failure



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November 27, 2018

Trends in First Gabapentin and Pregabalin Prescriptions in Primary Care in the United Kingdom, 1993-2017

François Montastruc, MD, PhD[1]; Simone Y. Loo, MSc[2]; Christel Renoux, MD, PhD[2]

JAMA®
The Journal of the American Medical Association

- **Contexte**
  - Gabapentine NEURONTIN° et Pregabaline LYRICA°
    - Signaux d'augmentation d'utilisation aux Etats-Unis
    - Risque de mésusage, d'addiction et overdose en particulier avec les opioïdes
      - UK : reclassés en substance C (≈ risque d'abus majeur »)

- **Objectif**
  - Estimer le taux de patients nouvellement traités par gabapentinoïdes en soins primaires au Royaume-Uni depuis leur commercialisation (1993 ou 2004)

CPRD

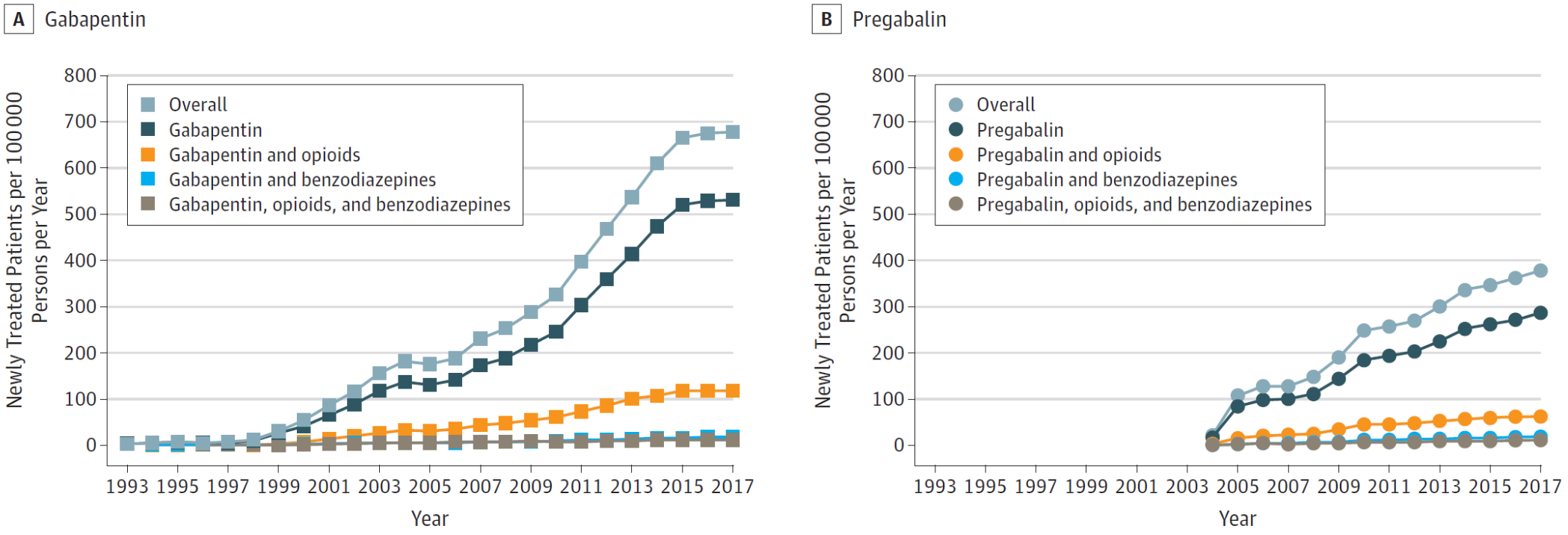
November 27, 2018

Trends in First Gabapentin and Pregabalin Prescriptions in Primary Care in the United Kingdom, 1993-2017

JAMA®
The Journal of the American Medical Association

François Montastruc, MD, PhD[1]; Simone Y. Loo, MSc[2]; Christel Renoux, MD, PhD[2]

Figure 1. New Users of Gabapentin and Pregabalin in the UK Primary Care System From 1993 to 2017



Rates of new users of gabapentin (A) and pregabalin (B) in the UK primary care system documented in the UK Clinical Practice Research Datalink from 1993 to 2017. Gabapentin and pregabalin were licensed in the United Kingdom in 1993 and 2004, respectively.

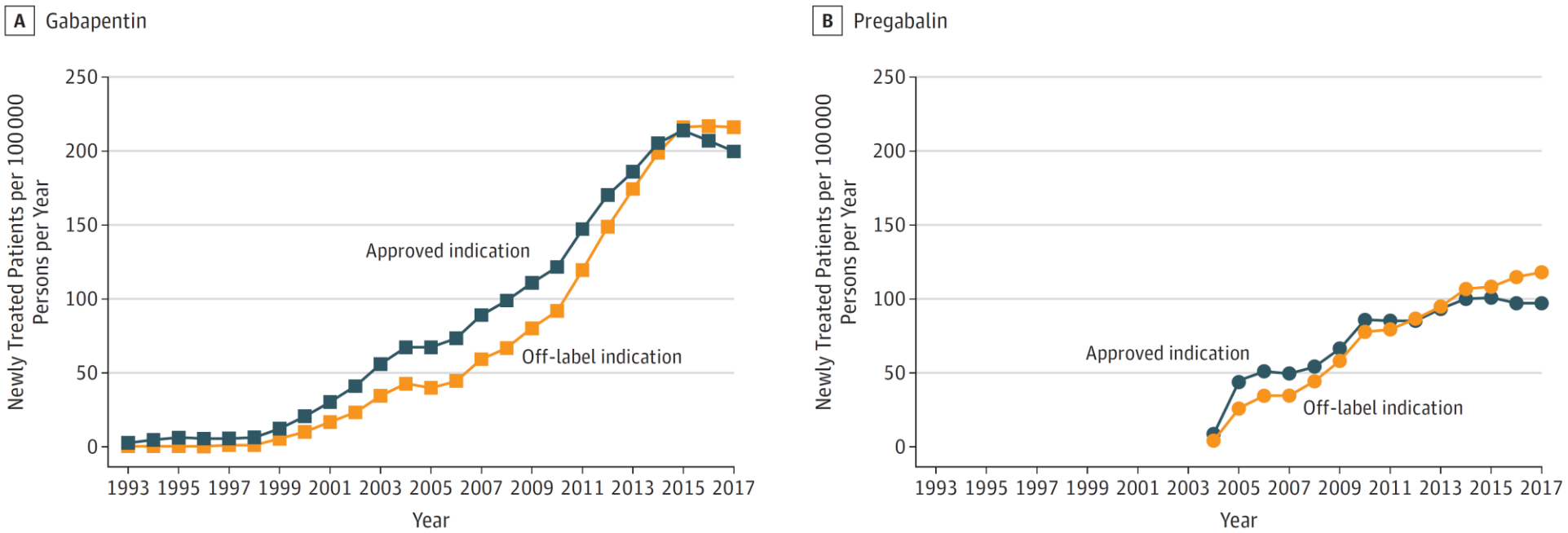
November 27, 2018

Trends in First Gabapentin and Pregabalin Prescriptions in Primary Care in the United Kingdom, 1993-2017

JAMA®
The Journal of the American Medical Association

François Montastruc, MD, PhD[1]; Simone Y. Loo, MSc[2]; Christel Renoux, MD, PhD[2]

Figure 2. New Users With a Gabapentin and Pregabalin Indication in the UK Primary Care System From 1993 to 2017



Rates of new users with an identified gabapentin (A) and pregabalin (B) indication documented in the UK Clinical Practice Research Datalink from 1993 to 2017. Approved gabapentinoid indications in the United Kingdom include epilepsy, neuropathic pain, migraines (gabapentin), and generalized anxiety disorder (pregabalin). Off-label indications were defined as nonneuropathic pain, migraines (pregabalin), generalized anxiety disorder (gabapentin), fibromyalgia, substance withdrawal, and others (eg, psychiatric disease, tremor, restless legs syndrome). Patients for whom a prescription indication could not be identified were not included.

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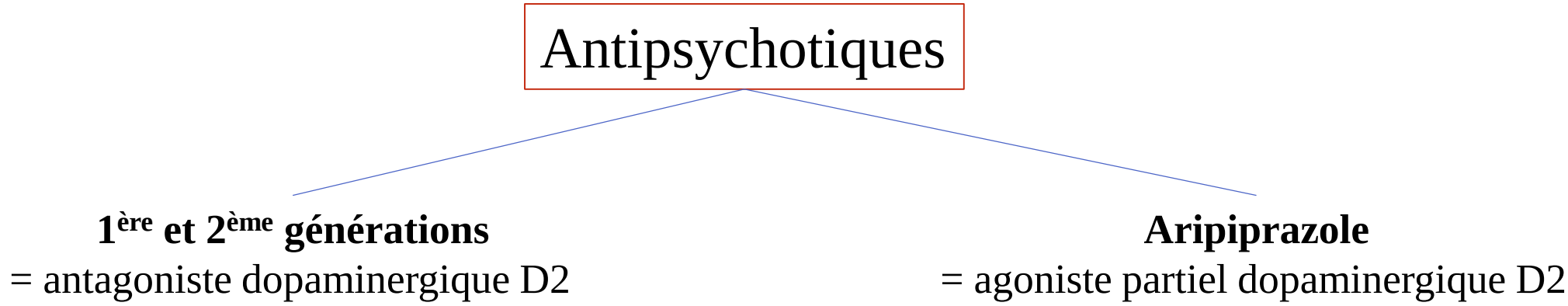
JAMA Psychiatry | Original Investigation

Association of Aripiprazole With the Risk for Psychiatric Hospitalization, Self-Harm, or Suicide

François Montastruc, MD, PhD; Rui Nie, MSc; Simone Loo, MSc; Soham Rej, MD, MSc; Sophie Dell'Aniello, MSc; Joëlle Micallef, MD, PhD; Samy Suissa, PhD; Christel Renoux, MD, PhD

Contexte

- **Psychopharmacologie clinique - CHU Toulouse**
  - Décompensations psychotiques ± sévérité lors de switch vers l'aripiprazole (ou l'ajout)



Contexte

- **Psychopharmacologie clinique - CHU Toulouse**
- **Signaux de pharmacovigilance en France**
  - Comité technique de pharmacovigilance

Contexte

- **Psychopharmacologie clinique - CHU Toulouse**
- **Signaux de pharmacovigilance en France**
  - Comité technique de pharmacovigilance
- **> 20 case reports**
- 1 méta-analyse

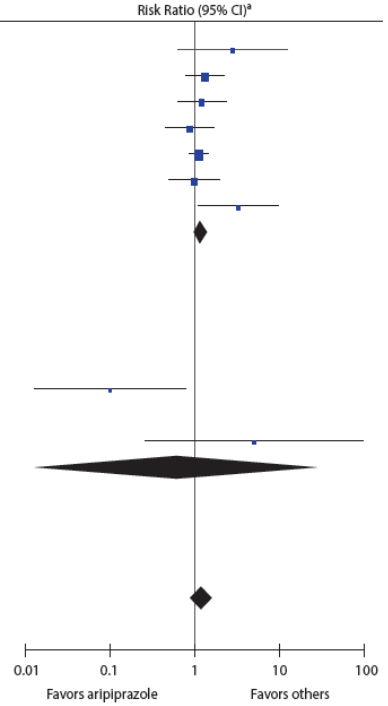
Can Aripiprazole Worsen Psychosis in Schizophrenia?

A Meta-Analysis of Double-Blind, Randomized, Controlled Trials

Hiroyoshi Takeuchi, MD, PhD[a,b,c,*]; Ali Fathi, MD[a];
Sadhana Thiyanavadivel[a,d]; Ofer Agid, MD[a,b,e]; and Gary Remington, MD, PhD, FRCPC[a,b,e,f]

Figure 2. Psychotic Worsening as an Adverse Event

Study or Subgroup	Aripiprazole Events	Aripiprazole Total	Other Antipsychotics Events	Other Antipsychotics Total	Weight	Risk Ratio (95% CI)[a]
Switching to aripiprazole						
Chan 2007[9]	8	49	2	34	3.7%	2.78 (0.63–12.27)
Fleischhacker 2009[10]	32	349	24	346	18.1%	1.32 (0.80–2.20)
Kane 2007[12]	18	153	14	144	13.3%	1.21 (0.63–2.34)
Kane 2009[13]	16	285	18	281	13.5%	0.88 (0.46–1.68)
Kasper 2003[14]	156	859	70	431	29.3%	1.12 (0.86–1.45)
Potkin 2003[18]	22	201	11	99	12.8%	0.99 (0.50–1.95)
Savitz 2015[19]	13	114	4	113	6.3%	3.22 (1.08–9.58)
Subtotal (95% CI)		**2,010**		**1,448**	**97.0%**	**1.17 (0.97–1.42)**
Total events	265		143			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_6 = 5.98$ ($P = .43$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.62$ ($P = .10$)						
Adding aripiprazole						
Kane 2009[26]	1	169	9	153	2.0%	0.10 (0.01–0.78)
Muscatello 2011[27]	0	14	0	17		Not estimable
Raghuthaman 2015[28]	2	15	0	15	1.0%	5.00 (0.26–96.13)
Subtotal (95% CI)		**198**		**185**	**3.0%**	**0.61 (0.01–27.75)**
Total events	3		9			
Heterogeneity: $\tau^2 = 5.94$; $\chi^2_1 = 4.52$ ($P = .03$); $I^2 = 78\%$						
Test for overall effect: $Z = 0.25$ ($P = .80$)						
Total (95% CI)		**2,208**		**1,633**	**100.0%**	**1.19 (0.88–1.60)**
Total events	268		152			
Heterogeneity: $\tau^2 = 0.06$; $\chi^2_8 = 12.36$ ($P = .14$); $I^2 = 35\%$						
Test for overall effect: $Z = 1.11$ ($P = .27$)						
Test for subgroup differences: $\chi^2_1 = 0.11$ ($P = .74$), $I^2 = 0\%$						

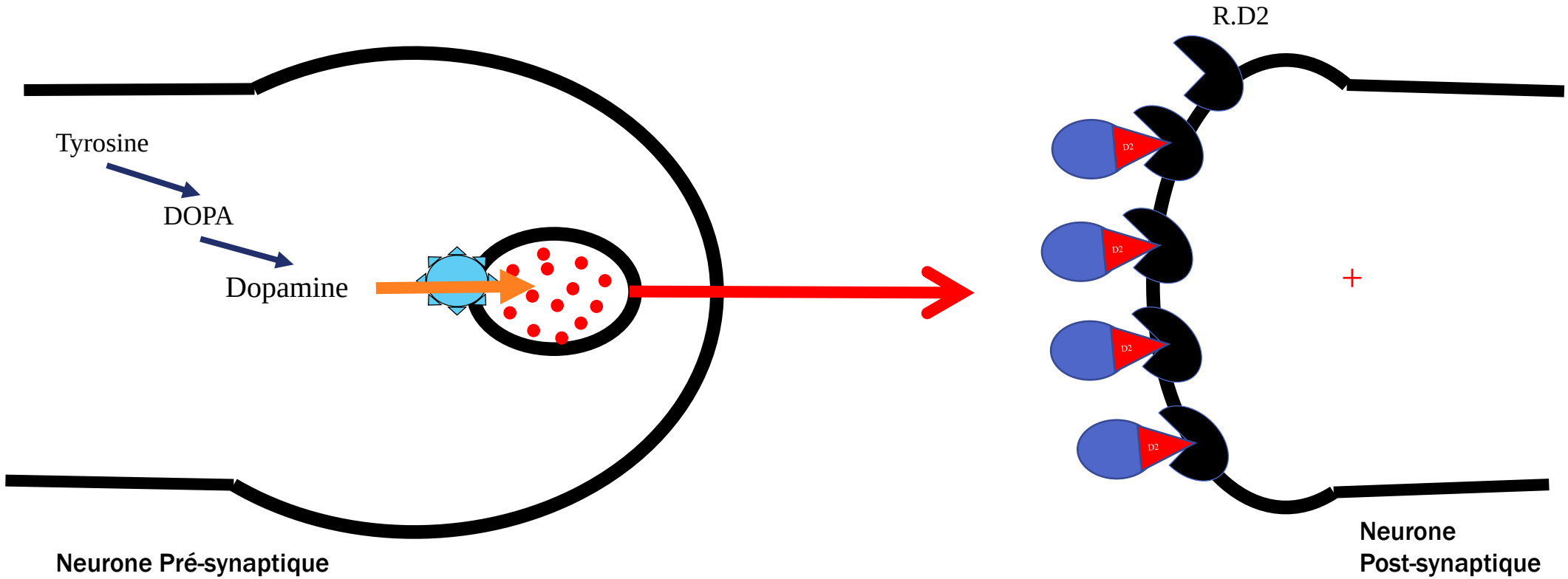


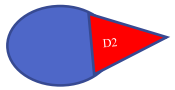
Contexte

- **Psychopharmacologie clinique - CHU Toulouse**
- **Signaux de pharmacovigilance en France**
  - Comité technique de pharmacovigilance
- **> 20 case reports**
- 1 méta-analyse

- **Plausibilité pharmacologique**

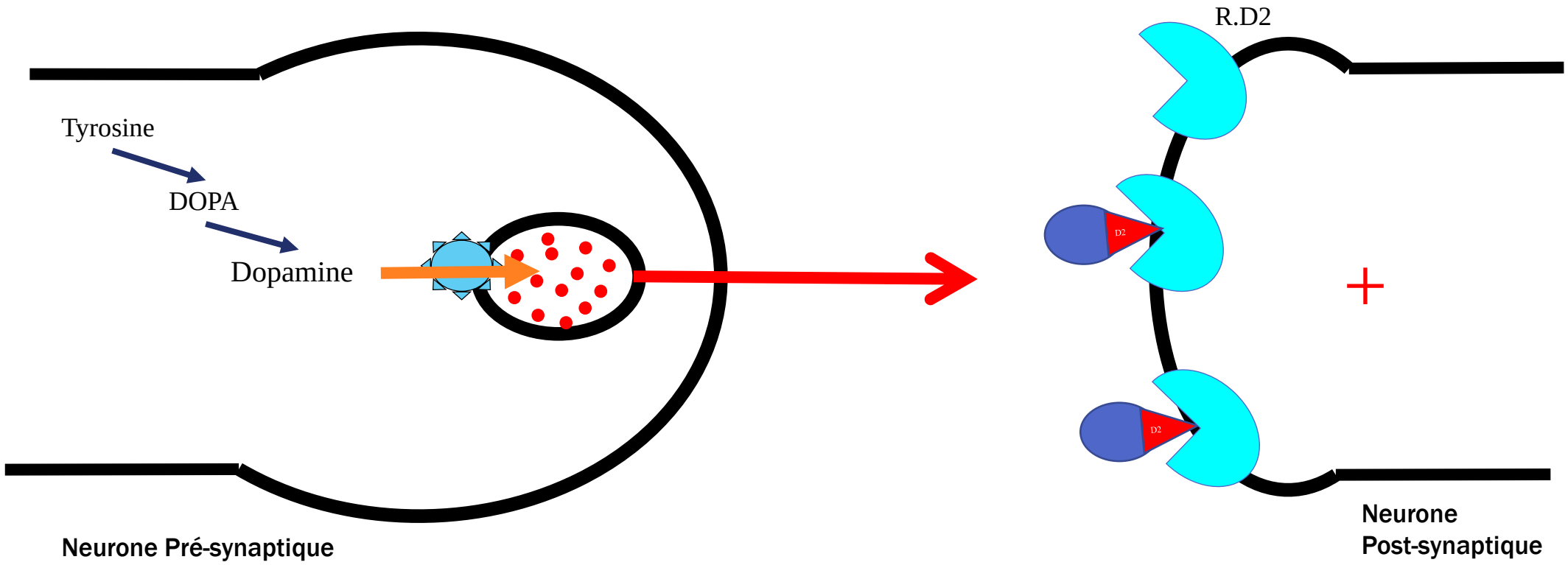
Hypothèse de mécanisme de l'hypersensibilité à l'aripiprazole

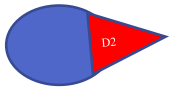




Neuroleptique = antagoniste D2

Hypothèse de mécanisme de l'hypersensibilité à l'aripiprazole

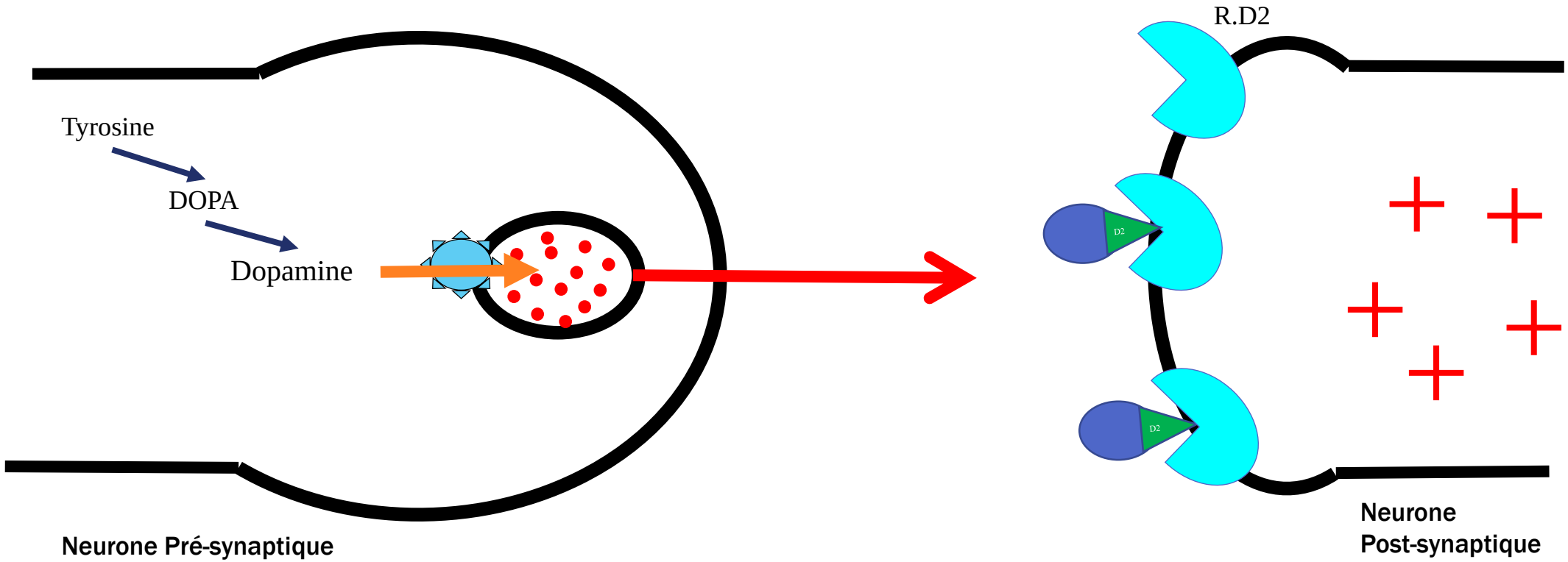


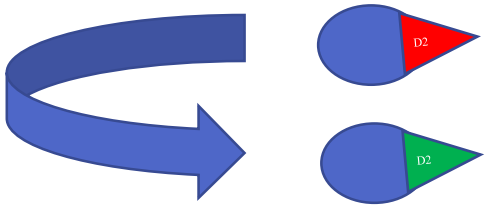


Neuroleptique = antagoniste D2 **<u>au long cours</u>**

Hypersensibilisation dopaminergique

Hypothèse de mécanisme de l'hypersensibilité à l'aripiprazole

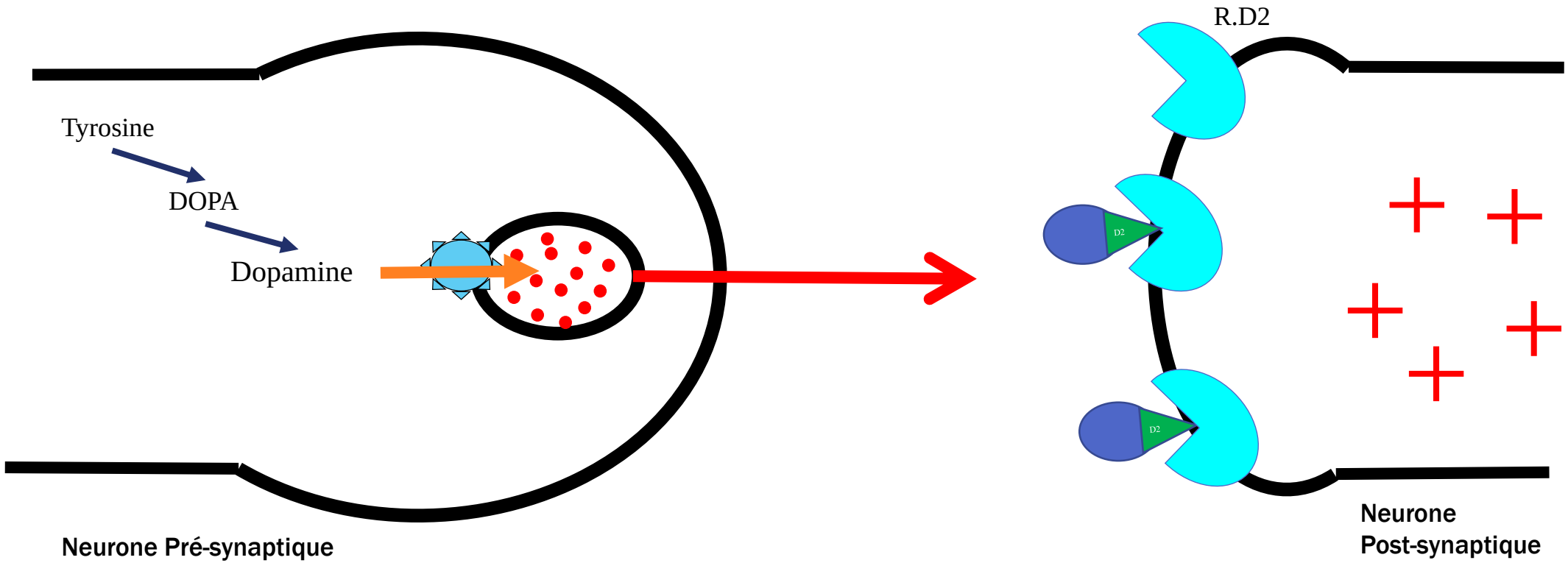


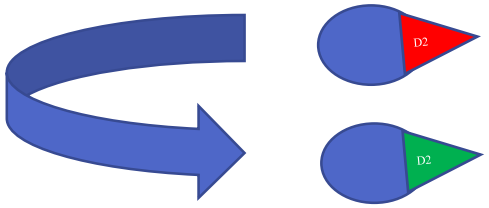


Neuroleptique = antagoniste D2 <u>au long cours</u>

Aripiprazole = agoniste partiel D2

Hypothèse de mécanisme de l'hypersensibilité à l'aripiprazole





Suractivation de la voie dopaminergique
=> « Psychose de supersensibilité »

Objectif

- Chez les patients préalablement exposés aux antipsychotiques

  - Passage à l'**aripiprazole** ou l'ajout de celui-ci
    - vs
  - Passage à **un autre antipsychotique** ou à l'ajout de celui-ci

<=> Cas graves d'échec du traitement psychiatrique

Méthodes – *Source de données*

- **CPRD**
  - Codes diagnostiques (Read Classification System)
  - Données démographiques
  - Mode de vie (tabac, alcool…)
  - Prescriptions médicamenteuses (BNF)

- chainé avec
  - **Hospital Episode Statistics HES**
    - Données hospitalières
    - Codes diagnostiques (ICD-10)
  - **Office for National Statistics (ONS)**
    - Données de mortalité (Suicides…)

Méthode – Population de l'étude
Cohorte de base

- Tous les patients ≥ 13 ans initiant un antipsychotique oral
  - **janvier 2005 – mars 2015**

- **Utilisateurs incidents**
  - Au moins 1 année d'enregistrement dans le CPRD avant l'entré dans la cohorte de base
  - Et sans prescription d'antipsychotique (oral ou injectable)

- Exclusion
  - Clozapine
  - 2 antipsychotiques
  - Parkinson et Alzheimer

Cohorte de base

Utilisateurs incidents

- 1 année CPRD avant l'entré dans la cohorte de base
- Et sans prescription d'antipsychotique

Méthode – Population de l'étude
Cohorte d'étude

- A partir de la cohorte de base
  - Identification des patients recevant l'aripiprazole ou un autre antipsychotique après le 1er Janvier 2005
  - Appariement 1:1
    - Chaque patient initiant l'aripiprazole
    - À un patient initiant un autre antipsychotique
  - Appariement
    - Année calendaire d'entrée dans la cohorte, durée depuis le premier antipsychotique prescrit, la pathologie psychiatrique (schizophrénie, troubles bipolaire, dépression…), âge
    - Time-conditional propensity score

→ Prevalent new-user design

Prevalent new–user design

- Habituellement en pharmaco-épidémiologie…
  - On utilise les **utilisateurs incidents** pour comparer 2 médicaments
    - Patients « naïfs »

- Mais problème pour évaluer les nouveaux médicaments par rapport aux anciens
  - Patients avec les nouveaux médicaments ont déjà utilisé l'ancien
    - **Exclusion d'un nombre important de patients +++**
      - **≠ « vraie vie »**

  - Exemple : inhibiteurs de DPP4 versus sulfamides hypoglycémiants

original article

Diabetes, Obesity and Metabolism 16: 1247–1256, 2014.

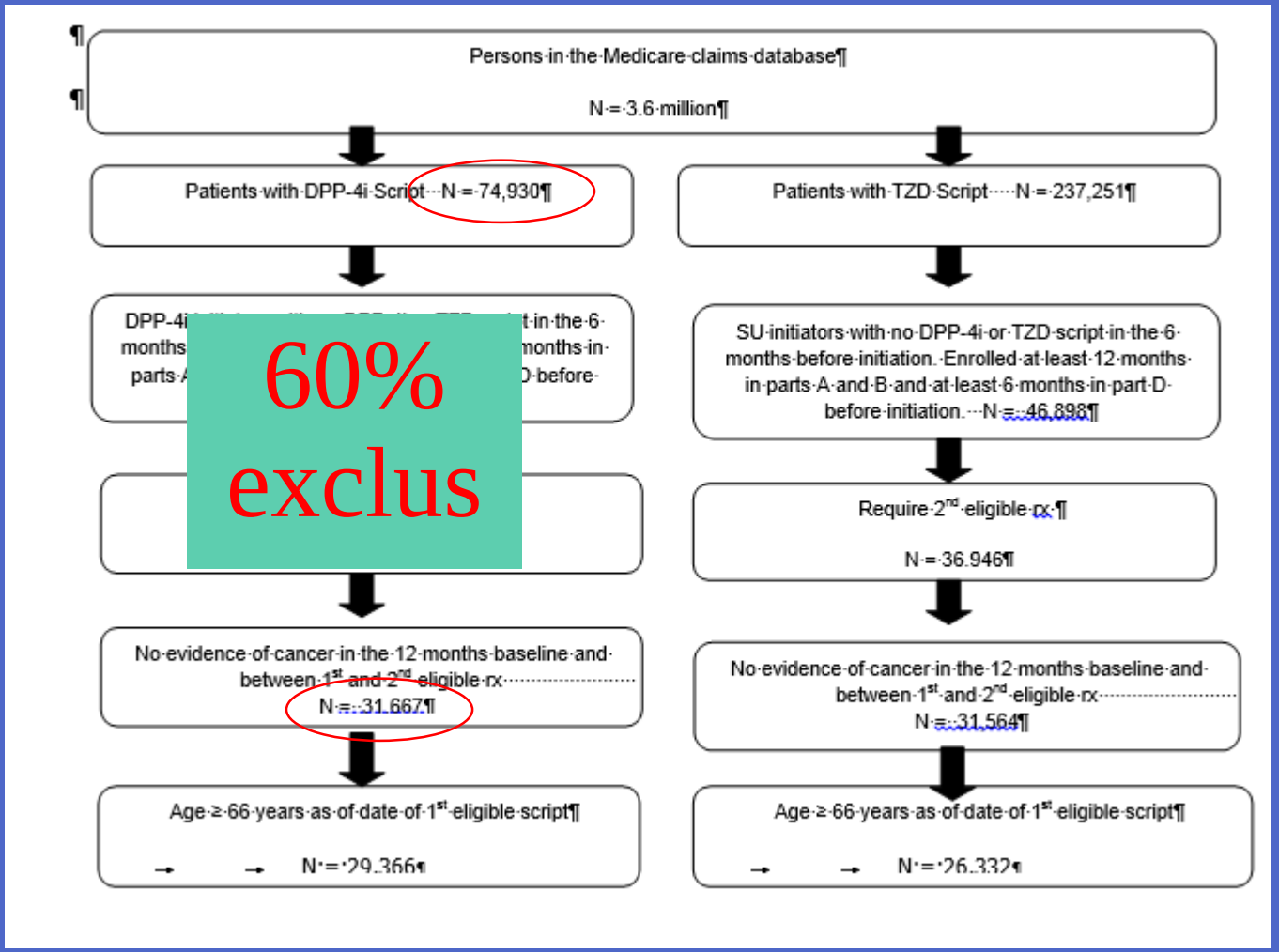
Dipeptidyl-peptidase-4 inhibitors and pancreatic cancer: a cohort study

M. Gokhale[1], J. B. Buse[2], C. L. Gray[1], V. Pate[1], M. A. Marquis[3] & T. Stürmer[1]

[1] *Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*
[2] *Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA*
[3] *Collaborative Studies Coordinating Center, Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

From this population, we identified two new-user active-comparator cohort pairs (Figures S1 and S2, Supporting Information) mimicking a clinical treatment decision: (i) patients initiating treatment with DPP-4 inhibitors versus treatment with SU (who had not been exposed to DPP-4 inhibitors or SU in the previous 6 months) and (ii) patients initiating DPP-4 inhibitor treatment versus those initiating TZD treatment (not exposed to DPP-4 inhibitors or TZD in the previous 6 months). Prevalent users in the 6 months before treatment initiation were excluded (for example, in the

New user design



PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2016)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4107

ORIGINAL REPORT

Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores

Samy Suissa[1,2,3]*, Erica E. M. Moodie[1] and Sophie Dell'Aniello[2,3]

[1] *Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada*
[2] *McGill Pharmacoepidemiology Research Unit, McGill University, Montreal, Quebec, Canada*
[3] *Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada*

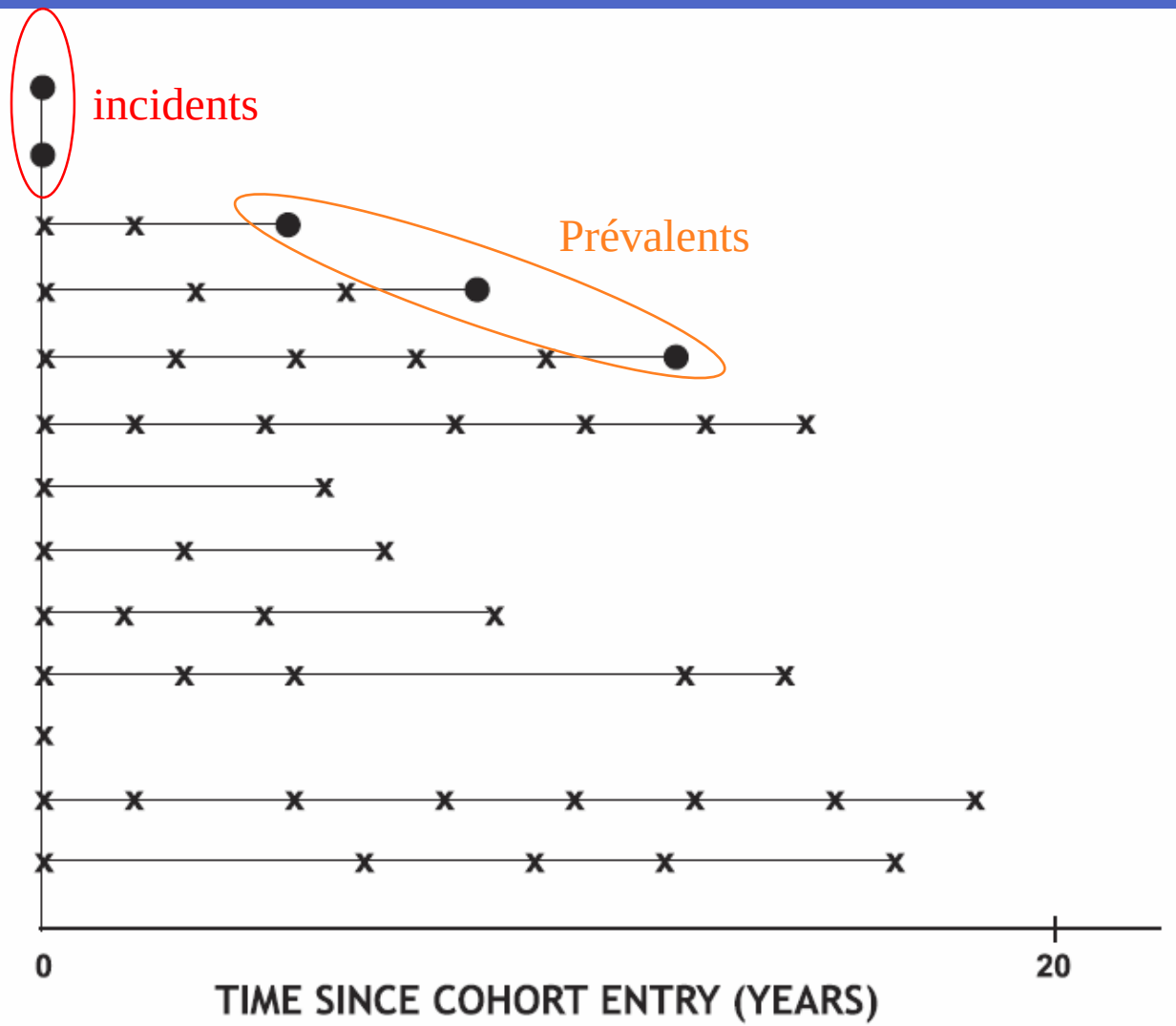


Figure 1. Depiction of a base cohort used for a prevalent new-user comparative study, formed of 13 subjects who initiated the comparator drug (each new prescription denoted by **x**) or the study drug (prescription denoted by ●), with cohort entry defined by the first such prescription

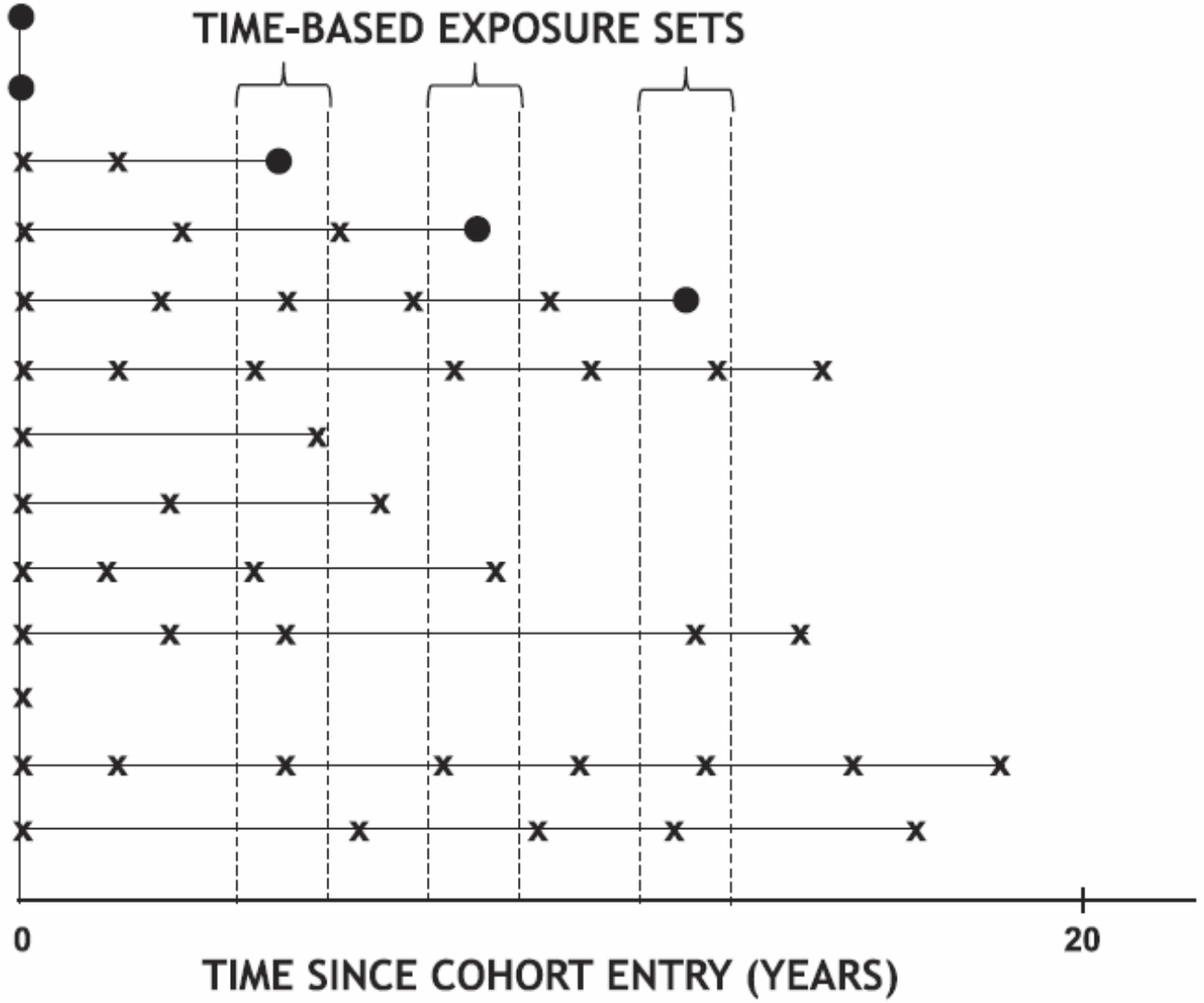


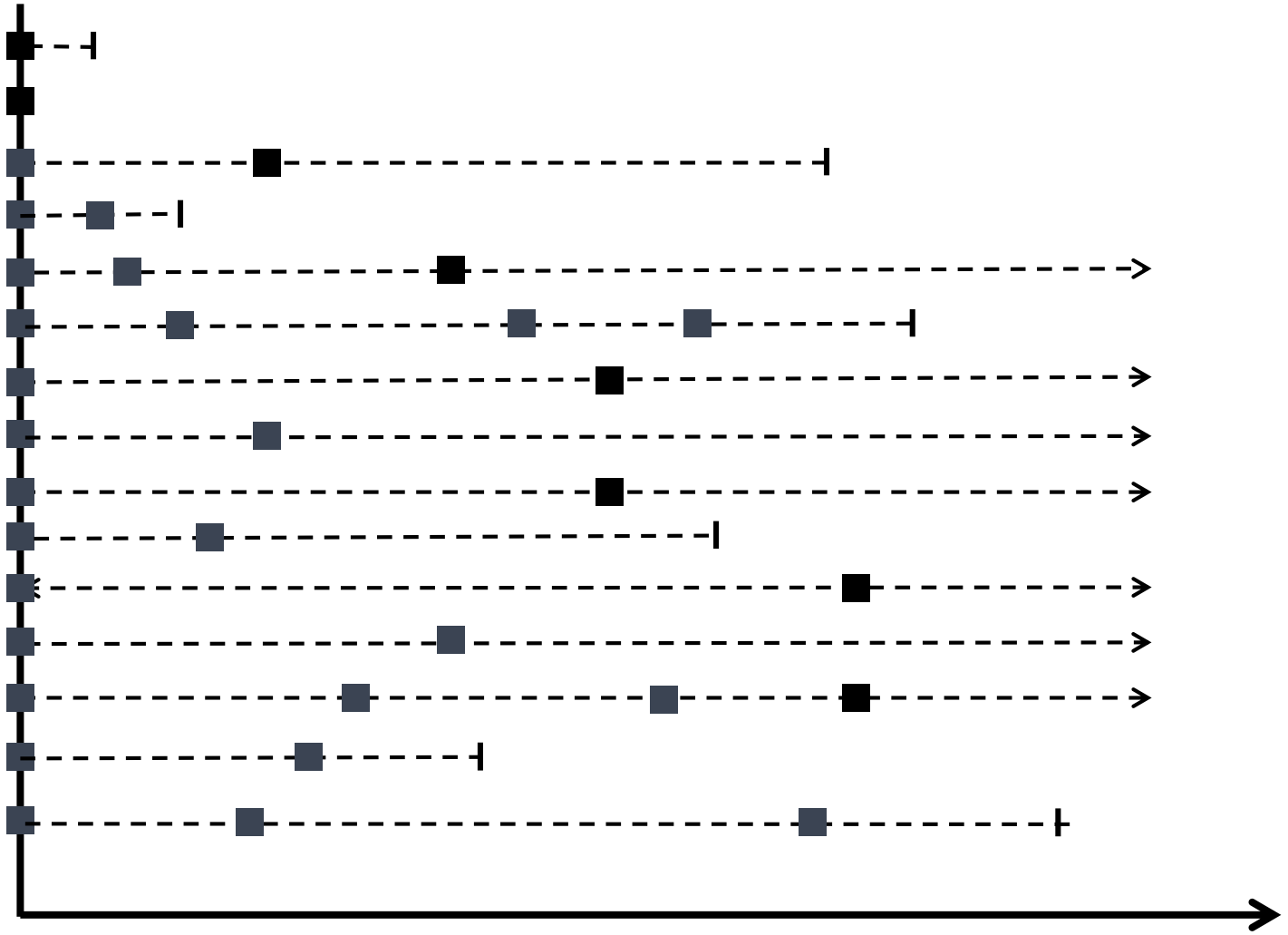
Figure 2. Depiction of a base cohort formed of 13 subjects with time-based exposure sets defined by a small time interval surrounding the timing of the new study drug prescription (●)

Méthode – Study Population
Cohorte d'étude

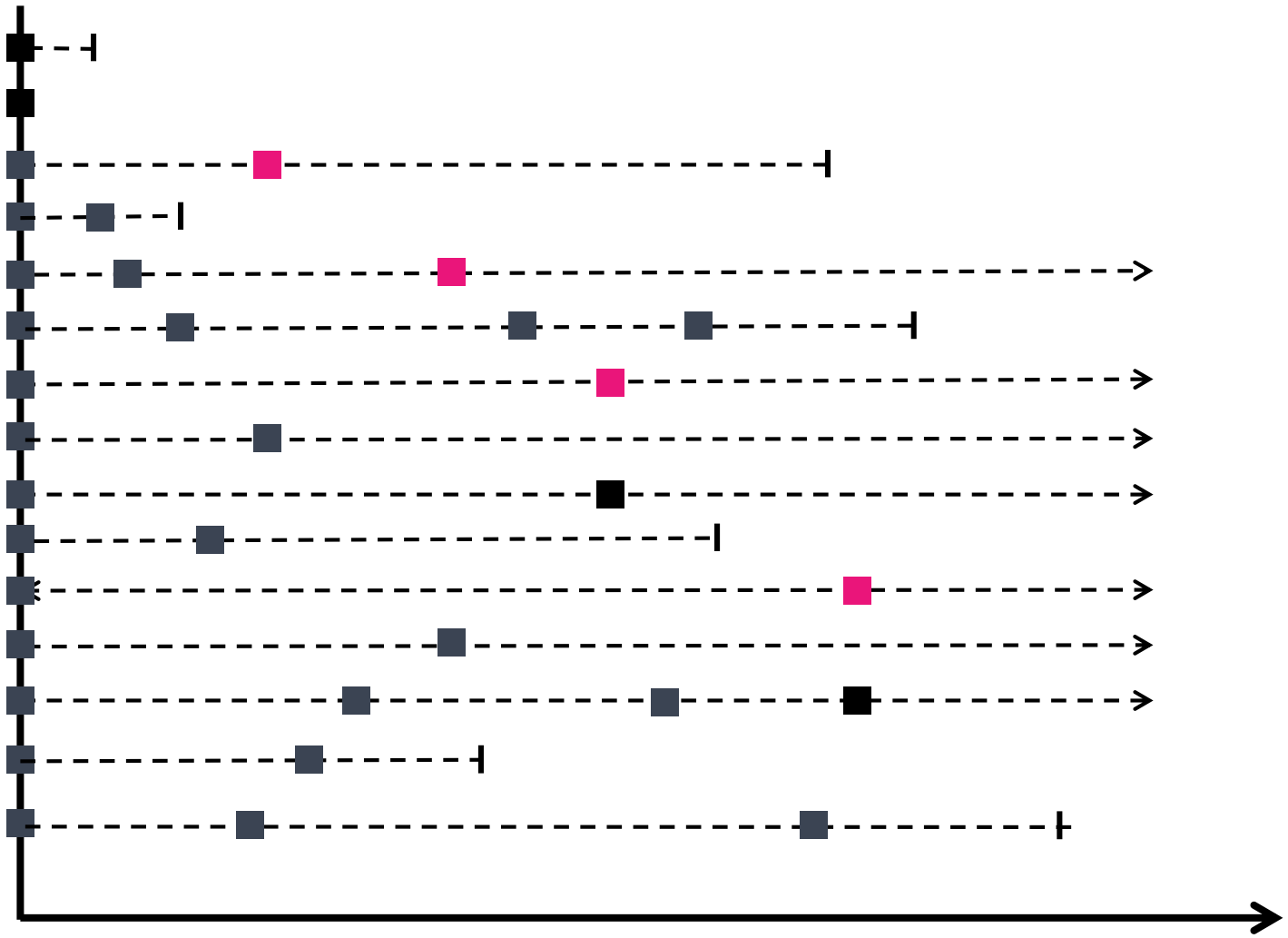
- A partir de la cohorte de base
  - Identification des patients recevant l'aripiprazole ou un autre antipsychotique après le 1er Janvier 2005
  - Appariement 1:1
    - Chaque patient initiant l'aripiprazole
    - À un patient initiant un autre antipsychotique
  - Appariement
    - Année calendaire d'entrée dans la cohorte, **durée depuis le premier antipsychotique prescrit**, la pathologie psychiatrique (schizophrénie, troubles bipolaire, dépression…), âge
    - Time-conditional propensity score

→ Prevalent new-user design

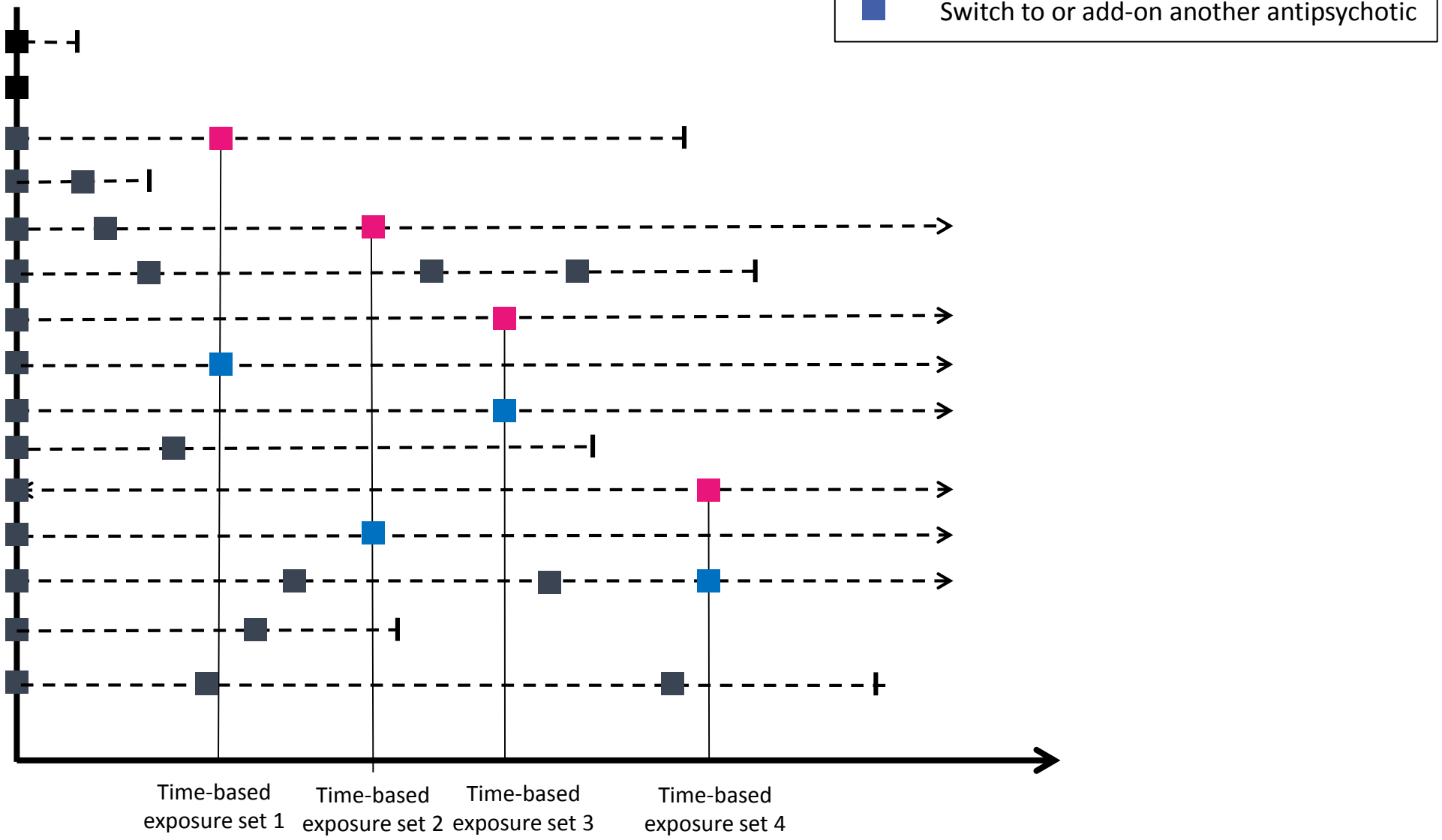
Cohorte d’étude



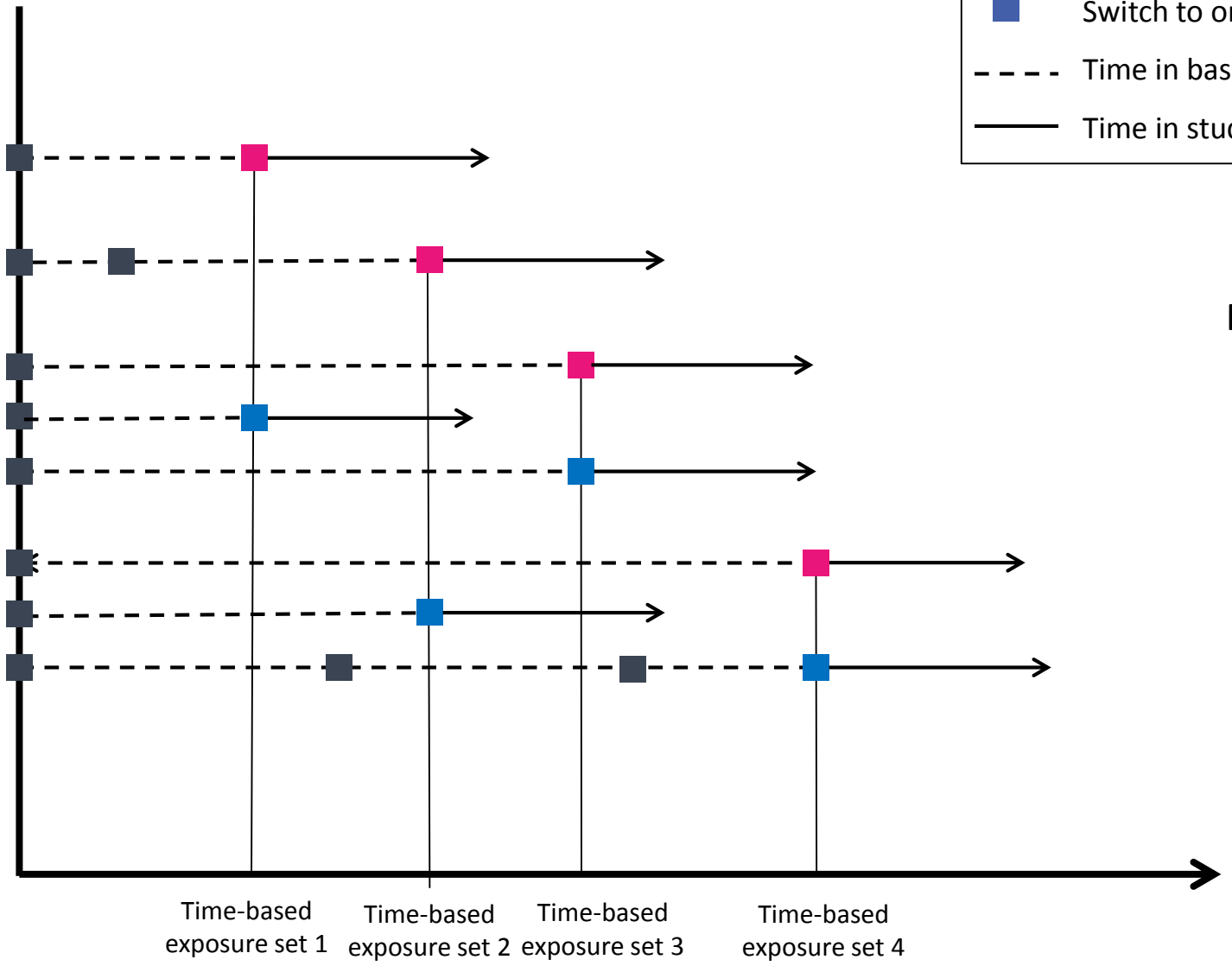
Cohorte d'étude



Cohorte d'étude



Cohorte d'étude



Pour identifier le patient comparateur le plus similaire

Time-conditional propensity score

Time-conditional propensity score

- “**Time-conditional** propensity score”
  - Dépend des variables dépendantes du temps mesurées au moment du « time based exposure set »
    - Et cela pour chaque exposure set

- Regression logistique conditionnelle
  - Pour estimer le score de propension
    - de l’exposition à l’aripiprazole par rapport à l’exposition à un autre antipsychotique

Suivi des patients

- Jusqu'à
  - Evénement « échec du traitement psychiatrique »
  - Pendant 1 an
  - Décès (autre cause que suicide)
  - Fin de l'enregistrement (CPRD) ou du chainage dans la base HES
  - Fin de la période d'étude 31 mars 2016
  - Première prescription de clozapine

Définition de l'exposition

- Aripiprazole oral
- Autres antipsychotiques oraux

- Approche **« en intention de traiter »** (ITT)
  - Exposés à l'antipsychotique de l'entrée dans la cohorte à la fin du suivi

- Analyse de sensibilité
  - Approche en « as treated »
    - Période de grâce de 30 jours

Définition de l’évènement

- **Décompensation psychotique**
  - Impossible à mesurer dans la CPRD +++

- **Evènement (composite)**
  - Hospitalisation en psychiatrie (base HES)
  - Tentative de suicide (base HES)
  - Suicide (base ONS)

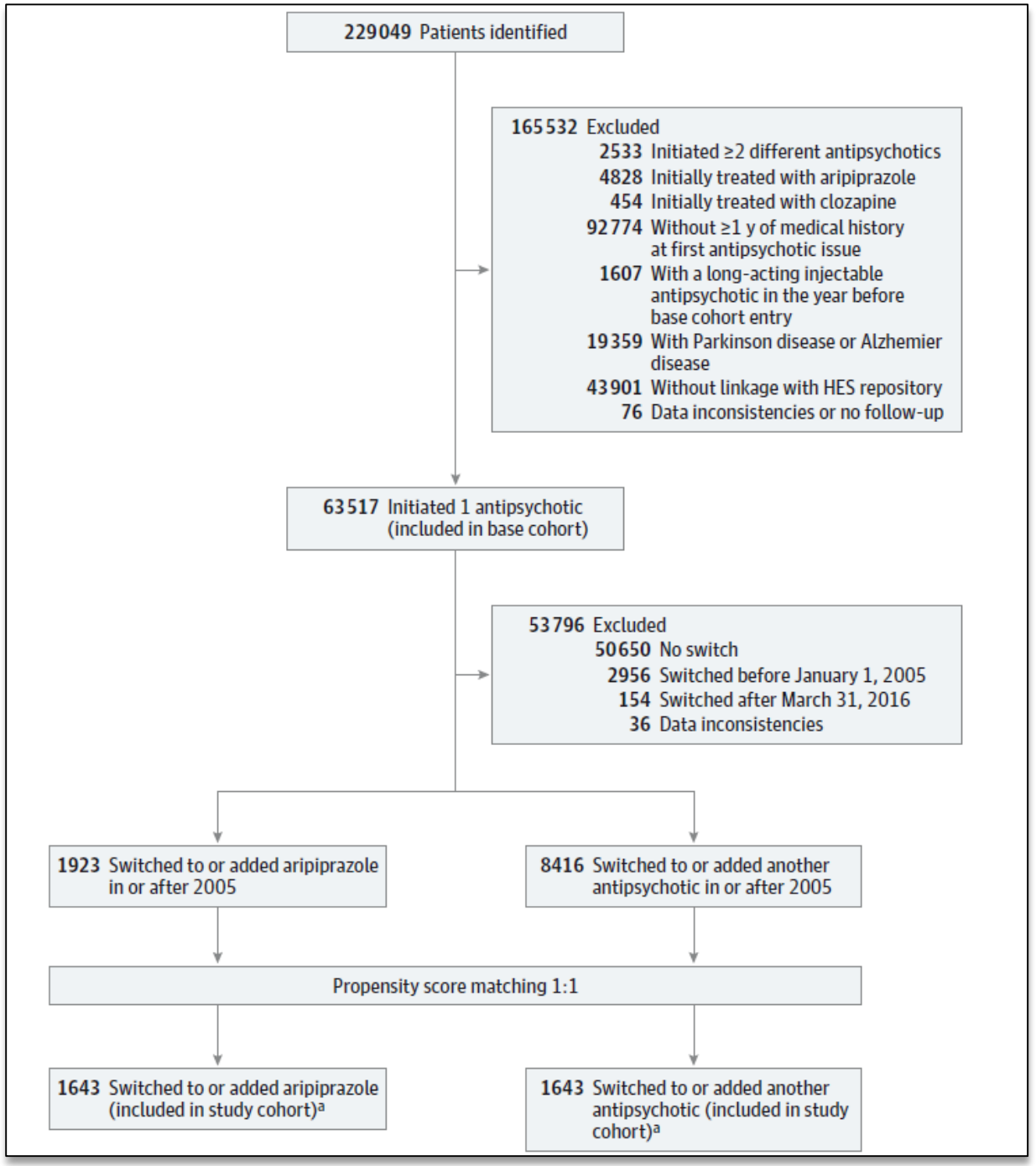
Analyse statistique

- Analyse descriptive

- Modèles de risques proportionnels de Cox (Hazard ratios HR) et intervalles de confiance à 95%
  - Pour l'hospitalisation en psychiatrie, tentative de suicide, suicide

- En plus de l'appariement
  - **Ajustement** sur l'âge, le nombre d'admission en psychiatrie dans le 6 mois précédent l'entrée dans la cohorte d'étude, le nombre d'antipsychotiques prescrits avant l'entrée dans la cohorte d'étude, et l'index de deprivation

Diagramme de flux



Variable	AP Prescription Used at Cohort Entry	
	Aripiprazole	Other AP Drug
All patients, No.	1643	1643
Age, mean (SD), y	42.1 (16.8)	42.4 (17.1)
Age group, y, No. (%)		
13-17	181 (11.0)	181 (11.0)
18-30	338 (20.6)	338 (20.6)
31-40	393 (23.9)	393 (23.9)
41-50	361 (22.0)	361 (22.0)
51-60	171 (10.4)	171 (10.4)
61-70	85 (5.2)	85 (5.2)
≥71	114 (6.9)	114 (6.9)
Male, No. (%)	694 (42.2)	772 (47.0)
Year of cohort entry, No. (%)		
2005-2008	439 (26.7)	509 (31.0)
2009-2011	554 (33.7)	599 (36.5)
2012-2016	650 (39.6)	535 (32.6)
Time since the first AP initiation, mean (SD), y	2.4 (2.5)	2.4 (2.5)
Comorbidities, No. (%)		
BMI, kg/m^2		
<25	459 (27.9)	452 (27.5)
25-30	397 (24.2)	398 (24.2)
>30	394 (24.0)	387 (23.6)
Unknown	393 (23.9)	406 (24.7)
Smoking status		
Never	465 (28.3)	494 (30.1)
Ever	1145 (69.7)	1112 (67.7)
Unknown	33 (2.0)	37 (2.3)
Alcohol abuse	102 (6.2)	92 (5.6)
Psychiatric diagnosis, No. (%)		
Schizophrenia	694 (42.2)	694 (42.2)
Bipolar disorder	220 (13.4)	220 (13.4)
Depression	325 (19.8)	325 (19.8)
Other psychiatric diagnoses[b]	37 (2.3)	37 (2.3)
Unknown	367 (22.3)	367 (22.3)
Coronary artery disease	33 (2.0)	32 (2.0)
Hypertension	127 (7.7)	109 (6.6)
Diabetes[c]	124 (7.6)	97 (5.9)
Hyperlipidemia	98 (6.0)	91 (5.5)
Stroke	33 (2.0)	28 (1.7)
Dementia	33 (2.0)	29 (1.8)
No. of psychiatric consultations, No. (%)[d]		
0	638 (38.8)	747 (45.5)
1-3	575 (35.0)	558 (34.0)
≥4	430 (26.2)	338 (20.6)
Self-harm	49 (3.0)	75 (4.6)
Most recent AP prescription before switch, No. (%)		
Olanzapine	581 (35.1)	479 (29.1)
Quetiapine fumarate	475 (28.7)	291 (17.7)
Risperidone	383 (23.1)	372 (22.6)
Haloperidol lactate	40 (2.4)	99 (6.0)
Chlorpromazine hydrochloride	36 (2.2)	102 (6.2)
FGA	156 (9.5)	446 (27.1)
SGA	1501 (91.4)	1201 (73.1)
Other psychotropic drugs, No. (%)[d]		
Antidepressants	1172 (71.3)	1137 (69.2)
Mood stabilizers	234 (14.2)	261 (15.9)
Sedative/hypnotics	524 (31.9)	544 (33.1)
ADHD medication	15 (0.9)	9 (0.6)
Drug used in alcohol dependence, No. (%)	18 (1.1)	18 (1.1)
Other drug type, No. (%)[d]		
Antihypertensive	332 (20.2)	312 (19.0)
Lipid lowering	210 (12.78)	185 (11.3)
Antiplatelet	133 (8.1)	117 (7.1)
Glucose lowering	93 (5.7)	77 (4.7)
Drug class, No. (%)[d]		
0-3	556 (33.8)	557 (33.9)
4-8	582 (35.4)	564 (34.3)
≥9	505 (30.7)	522 (31.8)

Tableau 1 Caractéristiques à l'entrée dans la cohorte

Table 2. Crude and Adjusted Hazard Ratios for the Association Between Starting Aripiprazole and the Risk of Psychiatric Treatment Failure

Exposure	No. of Psychiatric Events	Person-Years	Incidence Rate (95% CI)[a]	Matched HR	Adjusted HR (95% CI)[b]
Composite outcome[c]					
Other AP prescription	209	1307	15.98 (13.96-18.31)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	182	1384	13.15 (11.37-15.21)	0.83 (0.68-1.01)	0.87 (0.71-1.06)
Psychiatric hospitalization					
Other AP prescription	170	1327	12.81 (11.03-14.89)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	147	1404	10.47 (8.91-12.31)	0.83 (0.67-1.02)	0.85 (0.69-1.06)
Self-harm/suicide					
Other AP prescription	70	1388	5.04 (3.99-6.37)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	67	149	4.62 (3.64-5.87)	0.92 (0.66-1.29)	0.96 (0.68-1.36)

Abbreviations: AP, antipsychotic; HR, hazard ratio.

[a] Per 100 person-years.

[b] Adjusted for age, number of previous psychiatric admissions or self-harm in 6 months before cohort entry, number of different antipsychotic drugs before cohort entry, Index of Multiple Deprivation.

[c] Composite outcome comprises psychiatric hospitalization, self-harm, or suicide.

Table 3. Crude and Adjusted Hazard Ratios for the Association Between Starting Aripiprazole and the Risk of Psychiatric Treatment Failure (Secondar Analyses)

Subgroup	No. of Patients	No. of Psychiatric Events	Person-Years	Incidence Rate (95% CI)[a]	Matched HR (95% CI)	Adjusted HR (95% CI)[b]
No. of previous AP prescriptions						
1-3						
Other AP prescription	608	77	484	15.91 (12.73-19.90)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	426	43	359	11.99 (8.89-16.16)	0.76 (0.52-1.11)	0.81 (0.55-1.20)
4-12						
Other AP prescription	537	68	432	15.75 (12.41-19.97)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	581	53	500	10.60 (8.10-13.88)	0.68 (0.48-0.97)	0.68 (0.47-0.98)
≥13						
Other AP prescription	498	64	392	16.34 (12.79-20.87)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	636	86	525	16.37 (13.25-20.22)	1.01 (0.73-1.40)	1.05 (0.75-1.49)
Among patients exposed 3 mo before cohort entry						
Other AP prescription	861	109	681	16.00 (13.26-19.31)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	1054	115	896	12.83 (10.69-15.41)	0.81 (0.63-1.06)	0.87 (0.67-1.15)

Table 3. Crude and Adjusted Hazard Ratios for the Association Between Starting Aripiprazole and the Risk of Psychiatric Treatment Failure (Secondar Analyses)

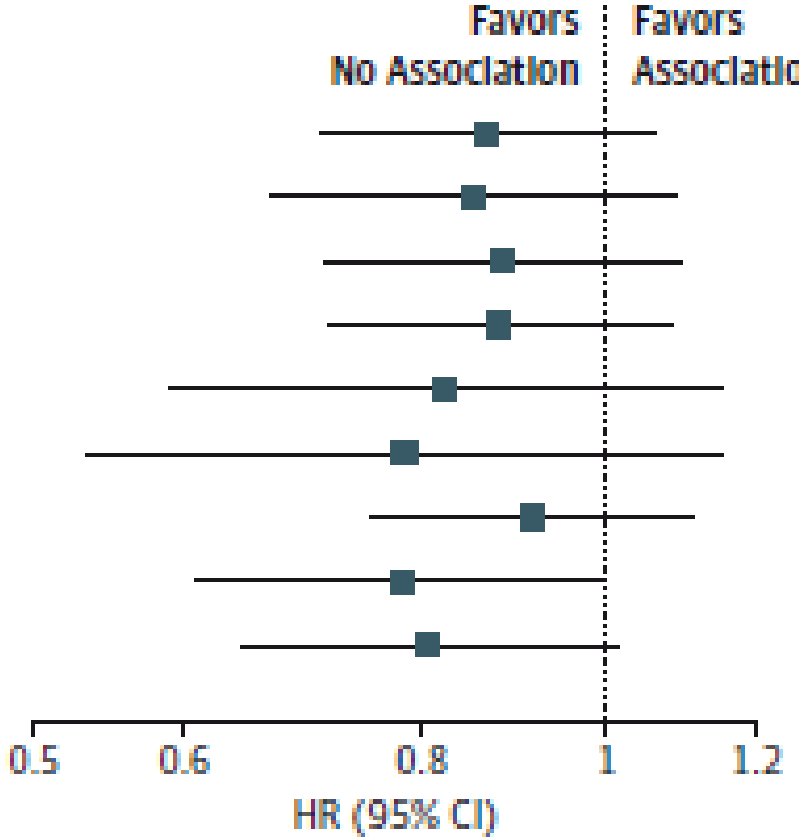
Subgroup	No. of Patients	No. of Psychiatric Events	Person-Years	Incidence Rate (95% CI)[a]	Matched HR (95% CI)	Adjusted HR (95% CI)[b]
DDD of the last antipsychotic prescribed before cohort entry						
≤1 DDD						
Other AP prescription	610	70	493	14.19 (11.23-17.94)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	778	71	665	10.67 (8.46-13.47)	0.76 (0.55-1.05)	0.82 (0.58-1.15)
>1 DDD						
Other AP prescription	251	39	188	20.74 (15.16-28.39)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	276	44	231	19.06 (14.18-25.61)	0.94 (0.61-1.44)	0.99 (0.62-1.58)
Among adults only						
Other AP prescription	1616	203	1288	15.76 (13.74-18.09)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	1611	179	1358	13.18 (11.38-15.26)	0.84 (0.69-1.03)	0.89 (0.72-1.09)
Among patients with schizophrenia						
Other AP prescription	694	119	532	22.38 (18.70-26.78)	1.00 [Reference]	1.00 [Reference]
Aripiprazole	694	95	582	16.33 (13.36-19.97)	0.74 (0.57-0.97)	0.82 (0.62-1.08)

Table 3. Crude and Adjusted Hazard Ratios for the Association Between Starting Aripiprazole and the Risk of Psychiatric Treatment Failure (Secondar Analyses)

Subgroup	No. of Patients	No. of Psychiatric Events	Person-Years	Incidence Rate (95% CI)[a]	Matched HR (95% CI)	Adjusted HR (95% CI)[b]
Switch or add-on AP drug						
Add-on[c]						
Other AP prescription	217	28	157	17.79 (12.28-25.76)	1 [Reference]	1 [Reference]
Aripiprazole	344	39	269	14.50 (10.59-19.84)	0.83 (0.51-1.33)	0.91 (0.56-1.48)
Switch						
Other AP prescription	1347	142	1018	13.94 (11.83-16.44)	1 [Reference]	1 [Reference]
Aripiprazole	1239	118	982	12.02 (10.03-14.39)	0.87 (0.68-1.11)	0.89 (0.68-1.15)

Figure 2. Forest Plot of the Association Between Switching to Aripiprazole and Psychiatric Treatment Failure

Sensitivity Analysis Cycle	HR (95% CI)
Primary analysis	0.87 (0.71-1.06)
Primary analysis with 6-mo follow-up	0.85 (0.67-1.09)
Study cohort after January 1, 2006	0.88 (0.71-1.09)
Users of SGAs	0.88 (0.72-1.08)
Hospitalization with a diagnosis of schizophrenia	0.82 (0.59-1.15)
Hospitalization with a diagnosis of mood disorders	0.78 (0.53-1.15)
Using Read Codes for self-harm and suicide	0.91 (0.75-1.11)
As-treated analysis (30-d grace period)	0.78 (0.61-1.00)
As-treated analysis (60-d grace period)	0.81 (0.64-1.01)



Discussion

- Chez les patients préalablement exposés à un antipsychotique
  - Pas de preuve en faveur d'une augmentation du risque d'échec de traitement psychiatrique associée
  - à l'initiation de l'aripiprazole
    - par rapport
  - À l'initiation d'un autre antipsychotique

- Résultats similaires dans les sous groupes
- Résultats similaires dans les analyses de sensibilités

Limites

- **Transférabilité**
  - CPRD = Base de soins primaires
    - Patients les plus sévères ?
    - Mais médecins généralistes au Royaume-Uni = rôle central
- **Biais de classification de l'exposition**
  - Observance médicamenteuse
  - Mais pas de différence entre les deux groupes
- **Evènement**
  - Hospitalisation en psychiatrie, tentative de suicide ou suicide
    - ≠
  - Décompensation psychotique
- **Biais de confusion**
  - Prescription de l'aripiprazole aux patients les moins sévères
  - Mais cohorte plutôt homogène avec les score de propension + ajustement

Conclusion

- Après une exposition aux antipsychotiques
  - L'initiation de l'aripiprazole peut-être associée à une aggravation psychiatrique

- **Mais**
  - Cette aggravation psychiatrique ne s'associe pas à un échec du traitement psychiatrique
    - Hospitalisation en psychiatrie, tentative de suicide ou suicide

- **Remarque**
  - Observations de pharmacovigilance ≠ résultats de pharmaco-épidémiologie

Plan

1. Mon parcours
2. Equipe de pharmaco-épidémiologie de McGill
3. Travaux effectués
    a. *Trends in First Gabapentin and Pregabalin Prescriptions in Primary Care in the United Kingdom, 1993-2017.*
    b. *Association of Aripiprazole With the Risk of Psychiatric Hospitalization, Self-Harm, or Suicide*
4. Collaborations
5. Conclusion

Evaluation du risque des médicaments
Approches multi-sources

BNPV

Cohortes
« cliniques »

VigiBase

EGB
SNDS

CPRD

Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study

Devin Abrahami,[1,2] Antonios Douros,[1,2,3] Hui Yin,[1] Oriana HY Yu,[1,4] Jean-Luc Faillie,[5] François Montastruc,[1,6] Robert W Platt,[1,2] Nathaniel Bouganim[7,8] Laurent Azoulay[1,2,8]

thebmj

BMJ 2018;363:k4880

CPRD

Table 2 | Crude and adjusted hazard ratios for association between use of DPP-4 inhibitors and GLP-1 receptor agonists and risk of cholangiocarcinoma

Exposure*	No of events	Person years	Incidence rate (95% CI)†	Crude hazard ratio	Adjusted hazard ratio (95% CI)‡
Other second or third line antidiabetic drugs	33	223 531	14.8 (10.2 to 20.7)	1.00	1.00 (reference)
DPP-4 inhibitors	27	103 362	26.1 (17.2 to 38.0)	1.70	1.77 (1.04 to 3.01)
GLP-1 receptor agonists	7	37 041	18.9 (7.6 to 38.9)	1.20	1.97 (0.83 to 4.66)

VigiBase

Table 3 | Reporting odds ratios of cholangiocarcinoma using World Health Organization VigiBase

Exposure	Cases*	Non-cases	ROR (95% CI)†
Sulfonylureas or thiazolidinediones	42	172 162	1.00 (reference)
DPP-4 inhibitors	34	54 870	1.63 (1.00 to 2.66)
GLP-1 receptor agonists	37	74 416	4.73 (2.95 to 7.58)
Negative control analysis			
Long acting insulin analogues	22	97 056	1.24 (0.72 to 2.15)

VigiBase

- Projet en cours : Abatacept - Cancer
  - Sibylle De Germay, Dr Haleh Bagheri, Pr Renoux

RHEUMATOLOGY

Original article

MarketScan

Abatacept initiation in rheumatoid arthritis and the risk of cancer: a population-based comparative cohort study

François Montastruc[1,2], Christel Renoux[1,3,4], Sophie Dell'Aniello[1], Teresa A. Simon[5], Laurent Azoulay[1,3,6], Marie Hudson[1,7] and Samy Suissa [1,3]

VigiBase

European Journal of Clinical Pharmacology (2018) 74:1181–1184
https://doi.org/10.1007/s00228-018-2496-3

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

CrossMark

Tamoxifen and the risk of Parkinsonism: a case/non-case study

François Montastruc[1,2,3,4] · Farzin Khosrow-Khavar[5,6] · Sibylle de Germay[1,2,7] · Christel Renoux[5,6,8] · Vanessa Rousseau[2,3,4,7] · Geneviève Durrieu[2,3] · Marion Montastruc[9] · Olivier Rascol[1,2,4,10] · Agnès Sommet[1,2,4,7,10] · Maryse Lapeyre-Mestre[1,2,4,7,10] · Justine Benevent[1,2,3,7] · Jean-Louis Montastruc[1,2,3,4,7,10]

CPRD

- Projet en cours : Tamoxifen - Parkinson
  - Pr Renoux, Pr Azoulay, M Farzin Khosrow-Kharvar

Conclusion

- Intérêt de l'expérience à l'étranger +++
  - Ouverture d'esprit, culture, rencontres…
  - Remise en question et apprentissage
  - Éclairage international

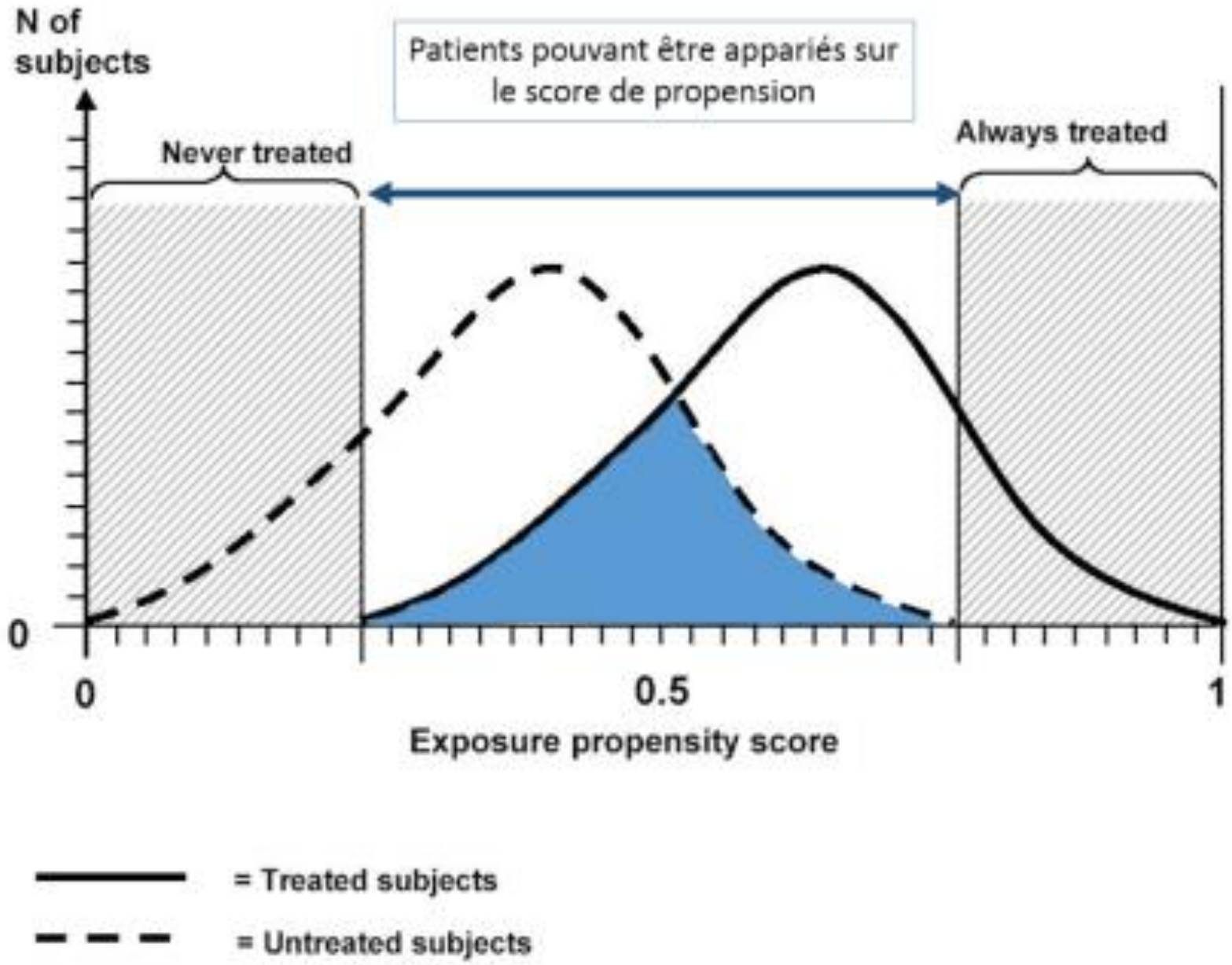
- Recherche
  - Collaborations
  - **Lecture critique d'article** +++ (Journal Club)

- Surveillance du risque médicamenteux
  - **Approches multi-sources et différentes méthodes**

Merci – Questions ?

Variables included in the propensity-score for exposure to aripiprazole versus other oral antipsychotics

Description	Variables
Patient characteristics	- Age (in categories) - Sex
Lifestyle habits*	- Body mass index (BMI) (< 25, 25-29, ≥ 30, Unknown) - Smokers (never, ever, unknown) - Alcohol abuse (yes/no)
Comorbidities*	- Coronary artery disease - Hypertension - Diabetes - Hyperlipidemia - Stroke - Dementia
History of antipsychotic prescriptions before cohort entry	- Number of antipsychotic prescriptions
Use of other psychotropic drugs*	- Antidepressants - Mood stabilizers (lithium, valproid acid, carbamazapine) - Sedative/hypnotics (mainly benzodiazepines) - ADHD medications - Drug used in alcohol dependence
Use of other drugs*	- Antihypertensive drugs - Lipid-lowering drugs - Antiplatelet drugs - Glucose lowering drugs - Nonsteroidal anti-inflammatory drugs (NSAIDs)


N of subjects
Patients pouvant être appariés sur le score de propension
Never treated
Always treated
0
0
0.5
1
Exposure propensity score
= Treated subjects
= Untreated subjects

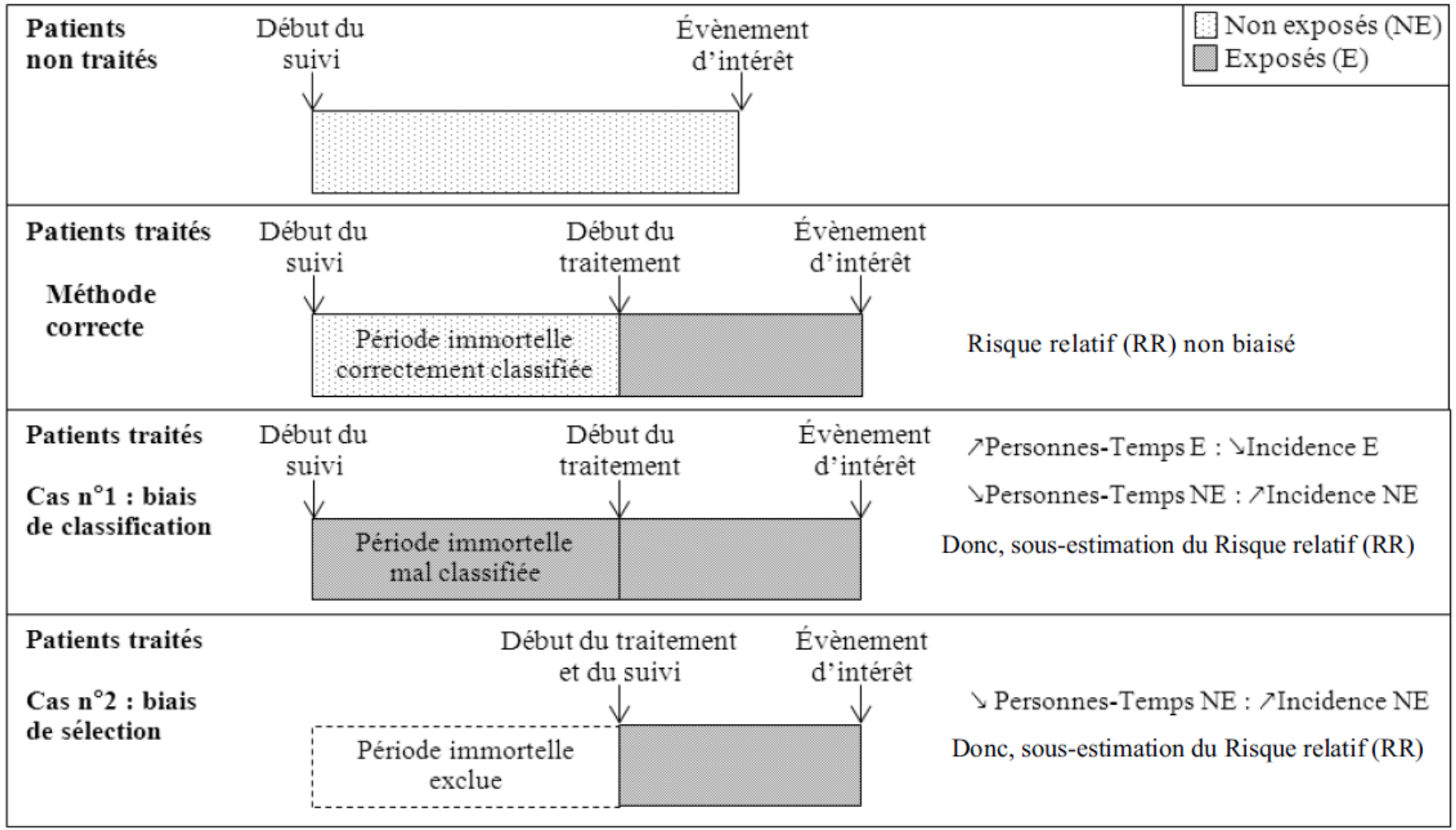


Fig. 1. Le biais de temps immortel survient lorsque la période entre le début du suivi et le début de l'exposition est considérée comme exposée (cas n° 1) ou est exclue (cas n° 2). D'après [26]