

## Electronic Supplementary Materials for *Drug Safety*

Surveillance of AntiDepressant Safety (SADS): Active signal detection of serious medical events following SSRI and SNRI initiation using big healthcare data

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**Table S1** Charlson comorbidities and other covariates

Covariate	Definition
<i>Charlson comorbidities</i>	
Diabetes without complication	ICD-8: 249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09 ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Diabetes with complications	ICD-8: 249.01-249.05, 249.08, 250.01-250.05, 250.08 ICD-10: E10.2-E10.8, E11.2-E11.8
Myocardial infarction	ICD-8: 410 ICD-10: I21, I22, I23
Peripheral vascular disease	ICD-8: 440-445 ICD-10: I70, I71, I72, I73, I74, I77
Congestive heart failure	ICD-8: 427.09, 427.10, 427.11, 427.19, 428.99, 782.49 ICD-10: I11.0, I13.0, I13.2, I50
Moderate/severe renal disease	ICD-8: 403, 404, 580-583, 584, 590.09, 593.19, 753.10-753.19, 792 ICD-10: I12, I13, N00-N05, N07, N11, N14, N17, N18, N19, Q61
Mild liver disease	ICD-8: 571, 573.01, 573.04 ICD-10: B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0
Moderate/severe liver disease	ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 456.00-456.09, 573.00 ICD-10: B15.0, B16.0, B16.2, B19.0, I85, K70.4, K72, K76.6
Cerebrovascular disease	ICD-8: 430-438 ICD-10: I60-I69, G45, G46
Chronic pulmonary disease	ICD-8: 490-493, 515-518 ICD-10: J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Cancer	ICD-8: 140-172, 174-194, 204-207, 195-199, 200-203, 204-207, 275.59 ICD-10: C00-C43, C45-C75, C76-C80, C81-C85, C88, C90, C91-C95, C96
Dementia	ICD-8: 290.09-290.19, 293.09 ICD-10: F00-F03, F05.1, G30
Connective tissue disease	ICD-8: 135.99, 446, 712, 716, 734 ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	ICD-8: 530.91, 530.98, 531-534 ICD-10: K22.1, K25-K28
Hemiplegia	ICD-8: 344 ICD-10: G81, G82
AIDS	ICD-8: 079.83 ICD-10: B21, B22, B23, B24
<i>Other</i>	
Alcohol-related diseases	ICD-8: 303, 570, 571.00, 571.10, 573.00, 573.01, 577.10, 979, 980 ICD-10: F10, T51, Z92.1, R78.0, K70, K71.1-K71.2, K86 ATC: N07BB
Hypertension	ICD-8: 400-404 ICD-10: I10-I13, I15
Dyslipidemia	ICD-8: 272 ICD-10: E78
Obesity	ICD-8: 277.99 ICD-10: E66 ATC: A08A
Schizophrenia and schizophrenia-related disorders	ICD-8: 295, 297, 298.3, 298.9, 299 ICD-10: F20-F23, F25, F28, F29
Bipolar affective disorder	ICD-8: 296.1, 296.3, 296.8 ICD-10: F30-F31
Anxiety disorder, including generalized anxiety disorder	ICD-8: 300.0, 300.2 ICD-10: F40-F41
Personal disorders	ICD-8: 301 ICD-10: F60
Unipolar depression	ICD-8: 296.0, 296.2 ICD-10: F32, F33
Other abuse	ICD-8: 304 ICD-10: F11-F19
Antipsychotics	ATC: N05A

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*AIDS* acquired immunodeficiency syndrome, *ATC* Anatomical Therapeutic Chemical, *ICD-8* International Classification of Diseases 8<sup>th</sup> revision, *ICD-10* International Classification of Diseases 10<sup>th</sup> revision

**Table S2** Parameters that can be tuned in the design and analysis

	Options				
	A	B	C	D	E
<i>Design choices</i>					
Data sources	<b>Single database/country</b>	Multiple databases/countries			
Study design	<b>Cohort study</b>	Case-control study			
Follow-up	1 month	3 months	<b>6 months</b>	1 year	
Population, age on the index date	<b>18 and above</b>	All ages	Children	Adolescents	Older adults
Comparator group	Unexposed	<b>Reference drug, e.g., citalopram</b>	<i>Reference of all other in the group except the exposure drug</i>	Reference drug group, e.g., antidepressants or antipsychotics	
Participants, washout	<b>New users</b>	Recurrent new users	Naïve users <sup>a</sup>	Recurrent naïve users	Prevalent users
Washout, time	6 months	<b>1 year</b>	2 years	5 years	Ever available in the data <sup>b</sup>
Washout, window	<b>Fixed date</b>	Moving window			
Exposure classification	<b>Intention-to-treat</b>	Time-dependent exposures	Cumulative exposure		
<i>Analysis choices</i>					
Outcome and covariate definition	<b>Broad, e.g. hepatotoxicity</b>	<b>Narrow, e.g. toxic liver disease</b>	<b>Specific, e.g. hepatic necrosis</b>		
Diagnosis type, outcome	<b>Primary diagnosis</b>	Primary and secondary diagnoses			
Type of hospitalization, outcome	<b>Inpatient</b>	In- and outpatient	In- and outpatient and emergency visits		
Statistical analysis	<b>Time-to-event, Cox</b>	Time-to-event, Poisson	Binary outcome logistic regression	Binary outcome, binomial regression	
Sequential interval	1 month	3 months	6 month	<b>1 year</b>	
Confounder adjustment	<b>Age and sex</b>	<b>Multivariate</b>	Propensity scores	Disease risk scores	Doubly robust estimation
Restriction	No restriction	<b>No previous outcome events</b>	No previous events associated with outcome		
Matching	<b>No matching</b>	Frequency	Individual	Covariate	Propensity score

Options in bold represent main choices in the study; Options in italic represents additional choices; <sup>a</sup>users who haven't used any antidepressants; <sup>b</sup>length of washout increases during the study

**Table S3** Outcome definitions

Medical event	ICD-10 codes
<i>Blood and lymphatic system disorders</i>	
Hemolytic anemia <sup>a</sup>	D59
AIHA <sup>a</sup>	D59.0, D59.1
Aplasia pure red cell <sup>a</sup>	D60
Aplastic anemia <sup>a, b</sup>	D61
ITP <sup>a</sup>	D69.3
Thrombocytopenia	D69.3-D69.6
Agranulocytosis <sup>a, c</sup>	D70
TTP <sup>a</sup>	M31.1
<i>Immune system disorders</i>	
Anaphylaxis <sup>a, d</sup>	T88.6, T78.2
<i>Psychiatric disorders</i>	
Hypomania	F30.0
Mania	F30
Hallucinations	R44
Delusions <sup>a</sup>	F22, F24, F23.3
Suicide	c_liste_49 = 48 <sup>j</sup>
Self-harm	X60-X84, Y10-Y34
<i>Nervous system disorders</i>	
Seizures/epilepsy	G40, G41
Hemorrhagic stroke	I60, I61
Ischemic stroke	I63, I64, G45.0, G45.1, G45.2, G45.3, G45.8, G45.9
PML <sup>a</sup>	A81.2
Polyneuropathy	G60.3, G60.8, G60.9, G62.0, G62.9
<i>Cardiac disorders</i>	
Arrhythmia <sup>a</sup>	I47-I49
Ventricular arrhythmia <sup>a</sup>	I47.2, I49.0, I49.3
Ventricular fibrillation <sup>a</sup>	I49.0
Myocardial infarction	I21-I22
Cardiomyopathies	I42
Cardiac arrest <sup>a, e</sup>	I46
Heart failure	I50
<i>Vascular disorders</i>	
Pulmonary hypertension <sup>a</sup>	I27.0
<i>Respiratory, thoracic, and mediastinal disorders</i>	
Pulmonary fibrosis <sup>a</sup>	J84
<i>Gastrointestinal disorders</i>	
Intestinal perforation <sup>a</sup>	K63.1
Pancreatitis acute <sup>a</sup>	K85
Pancreatitis acute, sensitivity	K85.0, K85.3, K85.8, K85.9
Autoimmune pancreatitis <sup>a</sup>	K86.1
Pancreatitis, all <sup>a</sup>	K85, K86.1
<i>Hepatobiliary disorders</i>	
Hepatotoxicity	K71, K72, K74.0, K75.2, K75.4, K75.9, K76.0, K76.2, K76.3, K76.4, K76.5, K76.6, K76.7, R74.0, E80.7
Toxic liver disease <sup>a, f</sup>	K71
Hepatic necrosis <sup>a</sup>	K71.1
Hepatic failure <sup>a</sup>	K72
Acute hepatic failure <sup>a, g</sup>	K72.0
Autoimmune hepatitis <sup>a</sup>	K75.4
Hepatic infarction <sup>a</sup>	K76.3
<i>Skin and subcutaneous tissue disorders</i>	
Dermatitis exfoliative <sup>a, h</sup>	L26
Erythema multiforme <sup>a</sup>	L51
Stevens-Johnson syndrome <sup>a</sup>	L51.1
Toxic epidermal necrolysis <sup>a</sup>	L51.2
Angio-neurotic edema <sup>a</sup>	T78.3

*Musculoskeletal and connective tissue disorders*

Fractures S02, S07, S12, S22, S32, S42, S52, S62, S72, S82, S92  
Myopathy<sup>a, i</sup> G72.0, G72.9

*Renal and urinary disorders*

Acute kidney injury<sup>a</sup> N17  
Renal failure<sup>a</sup> N17-N19  
Hyponatremia E87.1

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*AIHA* autoimmune hemolytic anemia, *ITP* immune thrombocytopenic purpura, *PML* progressive multifocal leukoencephalopathy, *TTP* thrombotic thrombocytopenic purpura

<sup>a</sup>Medical events from European Medicines Agency's Designated Medical Event list

<sup>b</sup>includes bone marrow failure and pancytopenia

<sup>c</sup>includes febrile neutropenia, granulocytopenia, neutropenic colitis, infections, and sepsis

<sup>d</sup>includes both anaphylactic and anaphylactoid shock/reaction

<sup>e</sup>includes sudden cardiac death

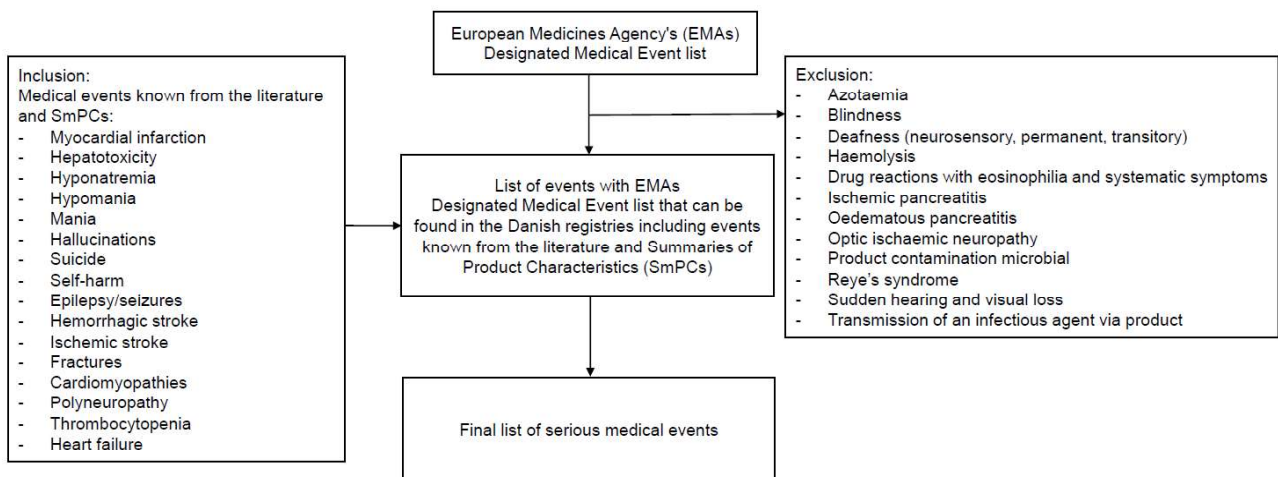
<sup>f</sup>includes drug-induced liver injury

<sup>g</sup>includes hepatitis fulminant and acute liver injury

<sup>h</sup>includes dermatitis exfoliative generalized

<sup>i</sup>includes rhabdomyolysis

<sup>j</sup>variable from the Cause of Death Register, c\_liste\_49 = 48 (suicide)



**Fig. S1** Selection of medical events from the European Medicines Agency's Designated Medical Event list, Summaries of Product Characteristics, and literature.

**Table S4** Potential safety signals detected in the surveillance system and corresponding events listed in Summaries of Product Characteristics (SmPCs)

<i>Drug</i>	Potential safety signal detected in surveillance system not listed in SmPCs	Detected in surveillance system and listed in SmPCs	Medical events listed in the SmPCs but not detected
<i>Duloxetine</i>		Suicides <sup>a</sup> Hyponatremia	Arrhythmia Epilepsy/seizures Anaphylaxis Hallucinations Mania
<i>Escitalopram</i>	Acute hepatic failure Acute kidney injury Cardiomyopathy Delusions Hepatic failure Hemorrhagic stroke ITP Intestinal perforation Renal failure	Hyponatremia	Angio-neurotic oedema Epilepsy/seizures Mania Hallucinations Self-harm <sup>a</sup> Thrombocytopenia Anaphylaxis Arrhythmia Ventricular arrhythmia Fractures
<i>Fluoxetine</i>	Delusions	Ventricular arrhythmia	Suicidal behaviour Thrombocytopenia Agranulocytosis Arrhythmia Epilepsy/seizures Hyponatremia Anaphylaxis Hypomania Mania Hallucinations Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis Angio-neurotic oedema
<i>Paroxetine</i>	Cardiomyopathy Delusions Polyneuropathy		Fractures Epilepsy/seizures Renal failure Thrombocytopenia Hyponatremia Self-harm <sup>a</sup> Hypomania Mania Hallucinations Heart failure Hepatic failure Anaphylaxis Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis
<i>Sertraline</i>	Heart failure Hepatic necrosis Toxic liver disease	Hepatotoxicity <sup>b</sup>	Angio-neurotic oedema Epilepsy/seizures Myocardial infarction Pancreatitis Hyponatremia Hallucinations Self-harm <sup>a</sup>



		Thrombocytopenia Arrhythmia Ventricular arrhythmia Anaphylaxis Stevens-Johnson syndrome Toxic epidermal necrolysis
<i>Venlafaxine</i> Pulmonary fibrosis	Arrhythmia <sup>c</sup> Hyponatremia Suicides <sup>a</sup>	Thrombocytopenia Mania Pancreatitis Epilepsy/seizures Ventricular arrhythmia Ventricular fibrillation Aplastic anemia Agranulocytose Anaphylaxis Hypomania Hallucinations Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis Angio-neurotic edema Myopathy
<i>Citalopram</i> Fractures Hepatic failure Ischemic stroke Renal failure	Cardiac arrest <sup>d</sup> Epilepsy/seizures	Angio-neurotic oedema Hallucinations Thrombocytopenia Anaphylaxis Arrhythmia Ventricular arrhythmia Hyponatremia Mania Self-harm <sup>a</sup>

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*ITP* immune thrombocytopenic purpura, *SmPCs* Summaries of Product Characteristics

<sup>a</sup>suicidal behaviour, <sup>b</sup>liver insufficiency/serious liver injury, <sup>c</sup>torsade de pointes, ventricular tachycardia, ventricular fibrillation, and QT prolongation, <sup>d</sup>QT prolongation;

**Table S5** Medical events and their appearance on the European Medicines Agency's Designated Medical Event list and Summaries of Product Characteristics of each of the investigated selective serotonin reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor

<i>Organ class</i> Medical event	European Medicines Agency's Designated Medical Event list	Citalopram	Escitalopram	Duloxetine	Venlafaxine	Fluoxetine	Sertraline	Paroxetine
<i>Blood and lymphatic system disorders</i>								
Hemolytic anemia	X							
AIHA	X							
Aplasia pure red cell	X							
Aplastic anemia	X				X			
ITP	X							
Thrombocytopenia		X	X		X	X	X	X
Agranulocytosis	X				X	X		
TTP	X							
<i>Immune system disorders</i>								
Anaphylaxis	X	X	X	X	X	X	X	X
<i>Psychiatric disorders</i>								
Hypomania					X	X		X
Mania		X	X	X	X	X		X
Hallucinations		X	X	X	X	X	X	X
Delusions	X							
Suicide		X	X	X	X	X	X	X
Self-harm		X	X	X	X	X	X	X
<i>Nervous system disorders</i>								
Seizures/epilepsy		X	X	X	X	X	X	X
Hemorrhagic stroke								
Ischemic stroke								
PML	X							
Polyneuropathy								
<i>Cardiac disorders</i>								
Arrhythmia	X	X	X	X	X	X	X	
Ventricular arrhythmia	X	X	X		X	X	X	
Ventricular fibrillation	X				X			
Myocardial infarction							X	
<i>Cardiomyopathies</i>								
Cardiac arrest	X	X						
Heart failure								
<i>Vascular disorders</i>								
Pulmonary hypertension	X							
<i>Respiratory, thoracic, and mediastinal disorders</i>								
Pulmonary fibrosis	X							
<i>Gastrointestinal disorders</i>								
Intestinal perforation	X							
Pancreatitis acute	X							
Pancreatitis acute, sensitivity								
Autoimmune pancreatitis	X							
Pancreatitis, all	X				X		X	
<i>Hepatobiliary disorders</i>								
Hepatotoxicity							X	
Toxic liver disease	X							
Hepatic necrosis	X							
Hepatic failure	X			X				X
Acute hepatic failure	X			X				
Autoimmune hepatitis	X							

Hepatic infarction	X								
<i>Skin and subcutaneous tissue disorders</i>									
Dermatitis exfoliative	X								
Erythema multiforme	X				X	X			X
Stevens-Johnson syndrome	X		X	X	X	X	X	X	X
Toxic epidermal necrolysis	X				X	X	X	X	X
Angio-neurotic edema	X	X	X	X	X	X	X	X	
<i>Musculoskeletal and connective tissue disorders</i>									
Fractures			X						X
Myopathy	X				X				
<i>Renal and urinary disorders</i>									
Acute kidney injury	X								
Renal failure	X								
Hyponatremia		X	X	X	X	X	X	X	X

*AIHA* autoimmune hemolytic anemia, *ITP* immune thrombocytopenic purpura, *PML* progressive multifocal leukoencephalopathy, *TTP* thrombotic thrombocytopenic purpura