

Supplemental Material

Use of tramadol and the risk of bleeding complications in patients on oral anticoagulants: A restricted review and meta-analysis

European Journal of Clinical Pharmacology

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Supplementary Table 1 Search strategies by database

Pubmed (<https://pubmed.ncbi.nlm.nih.gov/>)

Tramadol AND (Anticoagulants OR Acenocoumarol OR dicoumarol OR ethyl biscoumacetate OR phenprocoumon OR warfarin OR coumarin OR apixaban OR argatroban OR betrixaban OR eribaxaban OR otamixaban OR razaxaban OR rivaroxaban OR xabans OR dabigatran OR ximelagatran OR melagatran OR efegatran OR flovagatran OR inogatran OR napsagatran OR Vitamin K antagonists OR novel oral anticoagulants OR direct oral anticoagulants OR direct thrombin inhibitors OR factor Xa inhibitors OR VKA OR NOAC OR DOAC)

Embase (<https://www.embase.com/search/>)

Tramadol[ti,ab,kw] AND (Anticoagulants OR "anticoagulant agent" OR Acenocoumarol OR dicoumarol OR "ethyl biscoumacetate" OR phenprocoumon OR warfarin OR coumarin OR apixaban OR argatroban OR betrixaban OR eribaxaban OR otamixaban OR razaxaban OR rivaroxaban OR xabans OR dabigatran OR ximelagatran OR melagatran OR efegatran OR flovagatran OR inogatran OR napsagatran OR "Vitamin K antagonists" OR "novel oral anticoagulants" OR "direct oral anticoagulants" OR "direct thrombin inhibitors" OR "oral factor Xa inhibitors" OR VKA OR NOAC OR DOAC) AND bleeding

Supplementary Table 2 Characteristics of included case reports and case series

Author (year)	Study design	Number of cases	Patient demographics				Anticoagulant regimen	Tramadol regimen
			Age (years)	Sex	Comorbidities	Condition leading to tramadol intake		
Abadie et al (2013) [1]	Case series	13 (+ 2 with INR increase without bleeding)	71.6 (mean)	47% women	Not reported	Not reported	VKAs	Not reported
Adverse Drug Reactions Advisory Committee (2004) [2]	Case reports	2 (reported along 9 cases with INR elevation without bleeding)	76 and 88	Not reported	Not reported	Not reported	Warfarin	Not reported
Bouvy (1998) [3]	Case reports	1	88	Woman	Not reported	Not reported	Acenocoumarol	50 mg bid
		1	75	Woman	Not reported	Hip pain	Acenocoumarol	Not reported
Chiffolleau et al (2003) [4]	Case reports	2	77 and 86	Not reported	Not reported	Not reported	Fluindione	Not reported
Dong et al (2014) [5]	Case report	1	75	Woman	Paroxysmal atrial fibrillation Hypertension Diabetes mellitus type II	Osteoarthritis	Warfarin for atrial fibrillation	200 mg bid

Supplementary Table 2 (continued)

Author (year)	Concomitant medication(s)	Time to bleeding event	Bleeding complications	INR value	
				at admission	after tramadol or anticoagulant discontinuation
Abadie et al (2013) [1]	Not reported	Mean 5.9 days (SD 7,4)	Not reported	Not reported	Not reported
Adverse Drug Reactions Advisory Committee (2004) [2]	Not reported	In 11 patients with elevated INR or bleeding, median 4 days (range 3 to 7) except one case at 6 weeks	Death due to haemorrhagic stroke	5 in one case	Five reports describe rapid recovery within 1-4 days of withdrawal of tramadol with or without reduction in the dose of warfarin
Bouvy (1998) [3]	Carbasalate calcium 38 mg/day Omeprazole 20 mg/day Furosemide 40 mg/day	"Few days"	Nosebleed	High	Within therapeutic range
	Strumazol 10 mg bid Famotidine 20 mg bid Digoxin 0.25 mg/day Sertraline 50 mg bid Atenolol 100 mg/day Temazepam 20 mg bid Lactilol 5 g/day Glibenclamide 5 mg tid Paracetamol 500 mg once or twice a day	2 days	Hematoma	> 7	Not reported
Chiffolleau et al (2003) [4]	Not reported	"At tramadol introduction"	Hematoma	5.48 in one case	Not reported
Dong et al (2014) [5]	Amiodarone 200 mg/day Metoprolol 71.25 mg/day Fosinopril 10 mg/day Novolin 30R 6 IU before meals	3 days	Hematuria, ecchymosis	10.04	Within therapeutic range

Supplementary Table 2 (continued)

Author (year)	Study design	Number of cases	Patient demographics				Anticoagulant regimen	Tramadol regimen
			Age (years)	Sex	Comorbidities	Condition leading to tramadol intake		
Hedenmalm et al (2004) [6]	Case reports	1	74	Man	Not reported	Not reported	Warfarin	400 mg/day
		1	64	Man	Not reported	Not reported	Warfarin	400 mg/day
		1	58	Woman	Not reported	Not reported	Warfarin	50 mg/day
		3 patients without genotyping for cytochrome polymorphism	Between 58 and 89 years	Not reported	Not reported	Not reported	Warfarin	50 to 400 mg/day
Jensen (1997) [7]	Case report	1	84	Woman	Parkinson's disease	Not reported	Warfarin for pulmonary embolism	50 mg tid
Madsen et al (2004) [8]	Case report	1	54	Woman	None	Low back pain	Phenprocoumon for suspected deep venous thrombosis	50–100 mg qid
Sabbe et al (1998) [9]	Case report	1	61	Woman	Cerebrovascular accident Seizure disorder Hypothyroidism	Musculoskeletal pain	Warfarin for mitral valve replacement	50 mg qid

Supplementary Table 2 (continued)

Author (year)	Concomitant medication(s)	Time to bleeding event	Bleeding complications	INR value	
				at admission	after tramadol or anticoagulant discontinuation
Hedenmalm et al (2004) [6]	Digoxin, Furosemide, Prednisolone, Amiloride, Calcium carbonate, Zopiclon	Not specifically reported, but less than 60 days	Hematoma	Not reported	Not reported
	Salmeterol, Budesonide, Digoxin, Furosemide, Spironolactone, Metoprolol, Cyclizine, Paracetamol, Diazepam, Omeprazole, Lactulose	Not specifically reported, but less than 60 days	Hematoma	Not reported	Not reported
	Atorvastatin, Diltiazem, Losartan, Oestradiol, Norethisterone, Nitroglycerine, Fibers	Not specifically reported, but less than 60 days	Vaginal bleeding	Not reported	Not reported
	Not reported for the 3 patients without genotyping	Not specifically reported, but less than 60 days	Not reported	Not reported	Not reported
Jensen (1997) [7]	Diuretics Potassium supplements Spironolactone Levodopa/Benserazide	“Few days”	Gastrointestinal bleeding	Not reported	Not reported
Madsen et al (2004) [8]	Paracetamol 1 g qid	6 days	Nosebleed	4.0	Not applicable
Sabbe et al (1998) [9]	Digoxin 0,25 mg/day Phenytoin 100 mg tid Levothyroxine 100 µg/day Folic acid 1 mg/day	15 days	Arm ecchymosis	10.6	Within therapeutic range

Supplementary Table 2 (continued)

Author (year)	Study design	Number of cases	Patient demographics				Anticoagulant regimen	Tramadol regimen
			Age (years)	Sex	Comorbidities	Condition leading to tramadol intake		
Scher et al (1997) [10]	Case report	1	76	Man	Hypertension Benign prostatic hypertrophy Left bundle-branch block Degenerative joint disease	Neck arthritis	Warfarin for aortic valve replacement	50 mg tid
Stöllberger et al (2017) [11]	Case report	1	75	Man	Arterial hypertension Coronary artery disease Degenerative spondylopathy Hyperuricemia Paroxysmal atrial fibrillation Coxarthrosis Prostatic cancer Diabetes mellitus type II Gynecomastia	Chest pain	Dabigatran 150 mg bid for atrial fibrillation	100 mg/day
Vacher et al (2020) [12]	Case report	1	80	Woman	Not reported	Not reported	Fluindione	Not reported
Veltri et al (2019) [13]	Case report	1	86	Woman	Chronic atrial fibrillation Hypertension Diverticulosis Asthma	Neuropathic pain	Warfarin for atrial fibrillation	Not reported

Supplementary Table 2 (continued)

Author (year)	Concomitant medication(s)	Time to bleeding event	Bleeding complications	INR value	
				at admission	after tramadol or anticoagulant discontinuation
Scher et al (1997) [10]	Captopril 25 mg tid Hydrochlorothiazide/ triamterene daily	24 days	Blood blisters on toes	7.31	3.27
Stöllberger et al (2017) [11]	Valsartan 160 mg/day Amlodipine 5 mg/day Nicorandil 20 mg/day Furosemide 40 mg/day Atorvastatin 80 mg/day Bisoprolol 7.5 mg/day Metformin 2000 mg/day Tizanidine 2 mg/day Pantoprazole 40 mg/day Diclofenac and Naproxen up to four times per day	Unclear	Melena due to hemorrhagic gastritis Hemopericardium	Not applicable	Not applicable
Vacher et al (2020) [12]	Paracetamol	3 days	Fatal gastrointestinal bleeding	10	Not applicable
Veltri et al (2019) [13]	Not reported	Not reported	Rectal bleeding	5.4	1.9

BID, twice daily; *g*, grams; *INR*, international normalized ratio; *IU*, International Units; *mg*, milligrams; *QID*, four times daily; *QIW*, four times a week; *SD*, standard deviation; *TID*, three times daily; *TIW*, three times a week; *VKAs*, vitamin K antagonists

Supplementary File 1 Risk of bias assessment of case reports and case series, adapted from the Drug Interaction Probability Scale

- 1) Did the event match a classical picture of bleeding complications in patients on oral anticoagulants?
- 2) Were other possible causes of the clinical picture ruled out?
- 3) Did the patient have a previous history of uneventful oral anticoagulants intake at the same dose?
- 4) Did the symptoms occur within 30 days after tramadol prescription?
- 5) Did the INR or the bleeding complications remit upon withdrawal of tramadol and/or oral anticoagulants?
- 6) In case of oral anticoagulants readministration without tramadol, did the patient remain free of complication?

Supplementary Table 3 Risk of bias assessment of included case reports and case series

Author (year)	Did the event match a classical picture of bleeding complications in patients on oral anticoagulants?	Were other possible causes of the clinical picture ruled out?	Did the patient have a previous history of uneventful oral anticoagulants intake at the same dose?	Did the symptoms occur within 30 days after tramadol prescription?	Did the INR or the bleeding complications remit upon withdrawal of tramadol and/or oral anticoagulants?	In case of oral anticoagulants readministration without tramadol, did the patient remain free of complication?	Total score
Abadie et al (2013) [1]	Unknown	Unknown	Unknown	Most of the time	Unknown	Unknown	1
Adverse Drug Reactions Advisory Committee (2004) [2]	Yes	Unknown	Unknown	Yes (at least one case but possibly both < 8 days)	Unknown	Not applicable	1.5
Bouvy (1998) [3]	Yes	Unknown	Unknown	Yes	Yes / Unknown	Unknown	2.5
Chiffolleau et al (2003) [4]	Yes	Unknown	Unknown	Yes	Unknown	Unknown	2
Dong et al (2014) [5]	Yes	Yes	Yes	Yes	Yes	Unknown	5
Hedenmalm et al (2004) [6]	Yes	Unknown	Unknown	Uncertain	Unknown	Unknown	1
Jensen (1997) [7]	Yes	Unknown	Yes	Yes	Unknown	Unknown	3
Madsen et al (2004) [8]	Yes	Yes	No	Yes	Yes	Not applicable	4

Author (year)	Did the event match a classical picture of bleeding complications in patients on oral anticoagulants?	Were other possible causes of the clinical picture ruled out?	Did the patient have a previous history of uneventful oral anticoagulants intake at the same dose?	Did the symptoms occur within 30 days after tramadol prescription?	Did the INR or the bleeding complications remit upon withdrawal of tramadol and/or oral anticoagulants?	In case of oral anticoagulants readministration without tramadol, did the patient remain free of complication?	Total score
Sabbe et al (1998) [9]	Yes	Yes	Yes	Yes	Yes	Yes	6
Scher et al (1997) [10]	Yes	Yes	Yes	Yes	Yes	Yes	6
Stöllberger et al (2017) [11]	Yes	No	Yes	Unknown	Yes	Yes	4
Vacher et al (2020) [12]	Yes	Unknown	Unknown	Yes	Not applicable	Not applicable	2
Veltri et al (2019) [13]	Yes	Yes	Yes	Unknown	Yes	Yes	5

INR, international normalized ratio

Supplementary File 2 Newcastle-Ottawa quality assessment scale used for risk of bias assessment of case-control studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Is the definition of bleeding patients under anticoagulants adequate?
 - a) yes, with independent validation (2 independent sources or reference to primary records) ★
 - b) yes, eg record linkage or based on self reports
 - c) no description
- 2) Are bleeding patients representative
 - a) consecutive or obviously representative sample of bleeding patients under anticoagulants ★
 - b) potential for selection biases or not stated
- 3) Selection of nonbleeding patients under anticoagulants
 - a) same community as cases ★
 - b) hospital controls
 - c) no description
- 4) Definition of nonbleeding patients under anticoagulants
 - a) no history of bleeding under anticoagulants ★
 - b) no description of source

Comparability

- 1) Comparability of cases and controls on the basis of the design or analysis
 - a) study controls for age and sex ★
 - b) study controls for any additional factor ★

Exposure

- 1) Ascertainment of exposure to tramadol
 - a) secure record (eg pharmacy records) ★
 - b) structured interview where blind to case/control status ★
 - c) interview not blinded to case/control status
 - d) written self-report or medical record only
 - e) no description
- 2) Same method of ascertainment for exposure to tramadol for cases and controls
 - a) yes ★
 - b) no
- 3) Missing data on tramadol exposure
 - a) same rate for both groups ★
 - b) non respondents described
 - c) rate different and no designation

Supplementary Table 4 Risk of bias assessment of included case-control studies

Author (year)	Selection of cases and controls				Comparability of cases and controls		Ascertainment of exposure			Total stars
	Appropriate definition of bleeding patients under anticoagulants	Representativeness of bleeding patients under anticoagulants	Appropriate selection of nonbleeding patients under anticoagulants	Appropriate definition of nonbleeding patients under anticoagulants	Study controls for age and sex	Study controls for additional factors ^a	Appropriate ascertainment of exposure to tramadol	Same method of ascertainment for cases and controls	Same rate of missing exposure data for cases and controls	
Burgos-Gonzalez et al (2022) [14]	★	★	★	★	★	★ ^b	★	★	★	9
Launiainen et al (2010) [15]	★	no	★	★	no	no	★	★	★	6

^a Analyses or design controlling for at least one additional factor: history of gastrointestinal (GI) bleeding, diabetes, atrial fibrillation, chronic heart failure, chronic obstructive pulmonary disease, hypertension, renal impairment, hepatic impairment, stroke, anemia, cancer, alcohol use, NSAIDs, antiplatelet agents

^b Adjusted for body mass index, smoking status, arterial hypertension, renal and hepatic disorders, prior bleeds, gastrointestinal conditions, other medications (such as acid suppressing drugs, selective serotonin receptor inhibitors, VKAs, and other analgesics such as NSAIDs, codeine, and opioids)

Supplementary File 3 Newcastle-Ottawa quality assessment scale used for risk of bias assessment of cohort studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Representativeness of patients under anticoagulants and exposed to tramadol
 - a) truly representative of patients under anticoagulants exposed to tramadol in the community ★
 - b) somewhat representative of patients under anticoagulants exposed to tramadol in the community ★
 - c) selected group of patients under anticoagulants exposed to tramadol eg nurses, volunteers
 - d) no description of the derivation of the cohort
- 2) Selection of patients under anticoagulants and not exposed to tramadol
 - a) drawn from the same community as the exposed cohort ★
 - b) drawn from a different source
 - c) no description of the derivation of the non-exposed cohort
- 3) Ascertainment of exposure
 - a) secure record (eg pharmacy records) ★
 - b) structured interview ★
 - c) written self report
 - d) no description
- 4) Demonstration that bleeding occurred after exposition to tramadol
 - a) yes ★
 - b) no

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis
 - a) study controls for age ★
 - b) study controls for any additional factor ★

Outcome

- 1) Assessment of bleeding
 - a) independent blind assessment or reference to primary records ★
 - b) record linkage ★
 - c) self report
 - d) no description
- 2) Was follow-up long enough for outcomes to occur
 - a) yes (over one year) ★
 - b) no
- 3) Adequacy of follow up of cohorts
 - a) complete follow up - all subjects accounted for ★
 - b) subjects lost to follow up unlikely to introduce bias - < 10 % or described ★

c) follow up rate < 90 % and no description of those lost

d) no statement

Supplementary Table 5 Risk of bias assessment of included cohort studies

Author (year)	Selection of cohorts				Comparability of cohorts		Ascertainment of outcome			Total stars
	Exposed patients from a representative source population of patients under anticoagulants	Unexposed patients from the same source population as exposed patients	Appropriate ascertainment of exposure to tramadol	Demonstration that bleeding occurred after tramadol exposure	Study controls for age and sex	Study controls for additional factors ^a	Appropriate assessment of bleeding complications	Follow up at least one year	< 10% or adequate description of lost to follow up	
Penning-van Beest et al (2005) [16]	★	★	★	★	★	★ ^b	★	★	★	9
Vitry et al (2011) [17]	★	★	★	★	★	★ ^c	★	no	★	8

^a Analyses or design controlling for at least one additional factor: history of gastrointestinal (GI) bleeding, diabetes, atrial fibrillation, chronic heart failure, chronic obstructive pulmonary disease, hypertension, renal impairment, hepatic impairment, stroke, anemia, cancer, alcohol use, NSAIDs, antiplatelet agents

^b Adjusted for hypertension and history of GI bleeding

^c Adjusted for socio-economic index of disadvantage for postcode of residence, number of comorbidities, number of prescribers (annually), number of different pharmacies used (annually), previous bleeding related hospitalisations during the 1-year period before first warfarin prescription, number of different medicines prescribed during the study period (annually), residential status (annually) and if bleeding occurred in the first 2 weeks of warfarin initiation

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