Review Article

L-Type Calcium Channel Blockers, Extrapyramidal Symptoms, and Delirium: A Systematic Review of Case Reports

Dondapati Venkata Vamshi Krishna[1], Abhimanyu Velmurugan[1], A Sreeman Reddy[1], Aniket Shyam Kurmi[1], Satyam Sharma[1], Sankha Shubhra Chakrabarti[2], Upinder Kaur[3]

1. Banaras Hindu University, India; 2. Department of Geriatric Medicine, Banaras Hindu University, India; 3. Department of Pharmacology, Banaras Hindu University, India

Introduction: L-type voltage-gated calcium channels on dopaminergic neurons can regulate mental status and motor control. The potential of L-type calcium channel blockers (CCBs) to induce extrapyramidal symptoms (EPS) and delirium is scantily studied.

Methodology: A systematic review was conducted from June 2024 to August 2024 using Medline and Scopus on the published cases of EPS, delirium, and psychosis with CCBs.

Results: Out of 6908 articles screened, 20 studies involving 23 patients were selected. Fourteen cases of EPS (8 females) and nine cases of delirium or psychosis (6 males) were noticed. Nearly 80% of cases were reported in patients 60 years and above. EPS appeared after 1 day to 8.5 years of CCB administration and Parkinsonism was the commonest phenotype occurring after a median (Q1-Q3) time of 90 (60-360) days. The dihydropyridine (DHPs) class, particularly amlodipine, was implicated in the majority (n=8, 57.1%). Delirium was reported after a few hours to 7 days and psychosis was the commonest manifestation. Nifedipine (n=3), and diltiazem (n=4) were the common culprits. Nearly all patients improved after drug discontinuation, with a median recovery time of 14 days for EPS and 2 days for delirium.

Conclusion: L-type CCBs can induce EPS and delirium manifesting largely as psychosis. Older females might be the common victims of EPS and older males might be prone to delirium. Most cases have been associated with the dihydropyridine class and have been reversible. Prospective and well-controlled studies are needed to annotate the possible role of L-type CCBs in movement and mood disorders.

Dondapati Venkata Vamshi Krishna and Abhimanyu Velmurugan both contributed equally and should be considered as the first author.

A Sreeman Reddy and Aniket Shyam Kurmi both contributed equally.

Corresponding authors: SS Chakrabarti, sankha.chakrabarti1@bhu.ac.in; Upinder Kaur, drupinder.bhu@gmail.com

1. Introduction

Dopamine (D2 receptor) blockers and calcium channel blockers (CCBs) are the typical medication classes involved in drug-induced parkinsonism (DIP) and other extrapyramidal symptoms (EPS).[1][2] Flunarizine and cinnarizine are the T-type CCBs that have been linked with Parkinsonism, also known as De-melo Souza's syndrome.[2] T-type voltage-gated calcium channels are abundantly expressed on thalamic cortical neurons and basal ganglia structures.[3][4] The voltage-gated calcium channels are also known to modulate the pre-synaptic release of neurotransmitters such as dopamine and acetylcholine.[5][6] In addition to T-type calcium channels, the dopaminergic neurons of substantia nigra also display L-type voltage-gated calcium channels with multiple roles ranging from dopamine release to the regulation of D2 auto-receptors to producing intracellular calcium load and mitochondrial stress in neurons.[7][8][9]

The basis of the present review was the case of an elderly woman who was admitted to our department with a history of development of delirium within weeks of diltiazem administration. The delirium manifested initially as mental confusion and then progressed to insomnia and visual hallucinations which led to the administration of multiple antipsychotics. The lady then developed extrapyramidal features which persisted after discontinuation of antipsychotics and resolved fully only upon the discontinuation of diltiazem. Diltiazem is an L-type calcium channel blocker frequently used in the management of atrial arrhythmias and angina. The literature on the possible association of diltiazem with EPS and delirium is scanty. We systematically reviewed the available literature on the possible link between L-type CCBs and EPS and delirium.

 doi.org/10.32388/STCYS3

2. Methodology

2.1. Eligibility Criteria

We included all case reports of extrapyramidal disturbances associated with L-type CCBs and case reports of psychosis or delirium associated with L-type CCBs. Clinical studies other than case reports such as observational studies and clinical trials, review articles, in vitro studies, animal studies, viewpoints, or opinion papers were excluded. We also excluded articles not in the English language, those articles whose full text was unavailable, case reports with other disease phenotypes, and those with alternative drug doses.

2.2. Information Sources and Search Strategy

A comprehensive search was conducted in PubMed, and Scopus using individual keywords and appropriate MeSH terms. The review was initiated on 19th June 2024 and the final search was conducted on 22nd August 2024. Rayyan Systematic Review Management platform (Rayyan, MA, USA) was used for the removal of duplicates, screening of articles, and for finalizing the eligible articles.

2.3. Study Selection

Initial screening was done using the title and abstract. All eligible articles were scrutinized through full text. Additionally, relevant references cited in the articles were searched manually. In case of lack of clarity in the abstracts, the full text was analyzed. Authors UK, DVVK, AV, ASR, ASK, and SS conducted the screening. The conflict between any two authors on the eligibility or inclusion of articles was finally resolved by UK assisted by DVVK.

2.4. Data Collection Process and Data Items

UK and DVVK extracted the desired content from the articles in MS Word which was then transferred to MS Excel by AV and verified by UK and ASK. Data included author name, publication year, co-morbidities, demographics such as age and sex, concomitant drugs, type of calcium channel blocker (CCB), dose and duration of CCB, disease phenotype, individual symptoms, steps taken to manage the adverse event, outcomes of de-challenge, time for recovery and outcomes of rechallenge where available. Analysis of the included articles was done by UK assisted by AV, ASR, and SSC.

3. Results

A total of 7749 articles were identified through database search. After removing duplicates, 6968 articles were screened by title and abstract. After excluding 6908 articles not eligible for the present study due to reasons mentioned in the exclusion criteria, 60 articles were considered eligible for full study review. An additional 40 were removed in this process and the reasons are illustrated in **Figure 1**. A total of 20 articles including 22 patients were finally selected for the qualitative analysis[10][11][12][13][14][15][16][17][18][19][20] One female reported the occurrence of Parkinsonian features at two different times with two different CCBs and this was considered as two different cases[13] Thus 23 cases were reported in 12 males and 11 females with a median age (Q1-Q3) of 70 (62-76.5) years. The age of affected individuals varied from 24 years to 85 years with eighteen cases (78.3%) occurring in older adults of 60 years and above. Hypertension (15,65.2%), angina (6,26.1%), arrhythmias (4,17.4%), and diabetes (4,17.4%) were the common co-morbidities. The demographics and medical history of the selected cases are shown in **Table 1**.

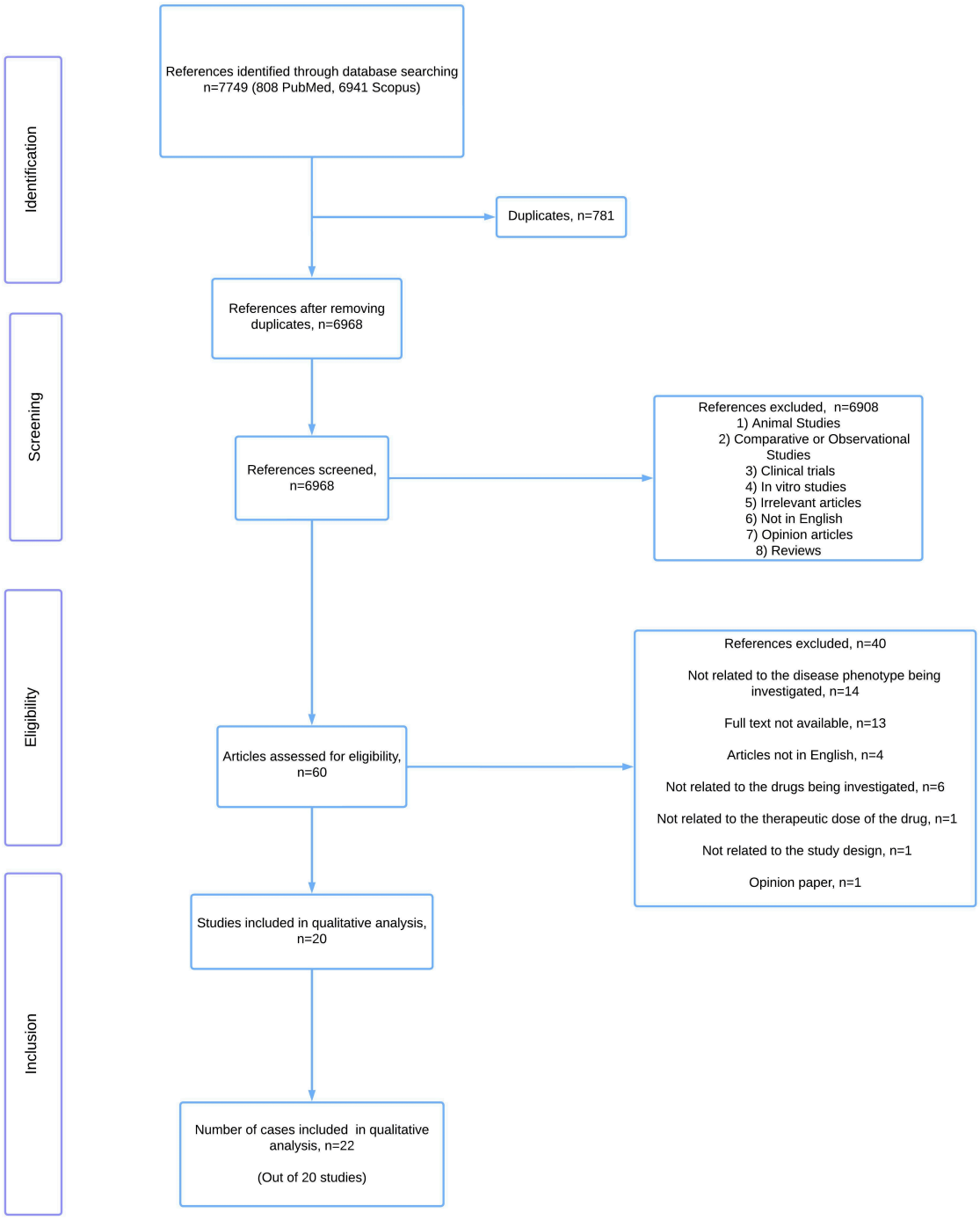

Figure 1. PRISMA flowchart of screening, inclusion, and selection of cases.

	Total cases, n=23	EPS cases, n=14	Delirium or psychosis, n=9
Male/female	12/11	6/8	6/3
Age Median (Q1-Q3)	70 (62-76.5)	71 (63.5-75.5)	66 (62-82)
Elderly (≥ 60 years)	18 (78.3)	11 (78.6)	7 (77.8)
Co-morbidities			
Hypertension	15 (65.2)	12 (85.7)	3 (33.3)
Angina	6 (26.1)	1 (7.1)	5 (55.5)
Diabetes	4 (17.4)	4 (28.6)	0
Arrhythmias	4 (17.4)	3 (21.4)	1 (11.1)
Coronary artery disease	3 (13.0)	2 (14.3)	1 (11.1)
Osteoporosis	2 (8.7)	2 (14.3)	0
Anxiety	2 (8.7)	2 (14.3)	0
Bipolar disorder	2 (8.7)	0	2 (22.2)
Renal disease	2 (8.7)	1 (7.1)	1 (11.1)
Concomitant drugs			
Angiotensin receptor blockers	3 (13.0)	3 (21.4)	0
Sulfonylureas	3 (13.0)	3 (21.4)	0
Beta-blockers	5 (21.7)	3 (21.4)	2 (22.2)
Nitrates	4 (17.4)	0	4 (44.4)
Phenotype noticed			
Parkinsonism	8 (34.8)	8 (57.1)	--
Dystonia	2 (8.7)	2 (14.3)	--
Akathisia	1 (4.3)	1 (7.1)	--
Tardive akathisia	1 (4.3)	1 (7.1)	--
Dystonia and akathisia	1 (4.3)	1 (7.1)	--
Parkinsonism and dystonia	1 (4.3)	1 (7.1)	--
Delirium	2 (8.7)	--	2 (22.2)
Psychosis	5 (21.7)	--	5 (55.5)
Delirium and psychosis	1 (4.3)	--	1 (11.1)
Mania	1(4.3)	---	1 (11.1)
Drugs implicated Dihydropyridines (Amlodipine, nifedipine) Benzothiazepines (diltiazem) Phenylalkylamines (verapamil)	12 (7,5) 7 4	8 (6,2) 3 3	4 (1,3) 4 1
Time of onset Range Median (Q1-Q3) (in days)	NA	1 day – 8.5 years 75 (14.5-300) (For Parkinsonism) 90 (60-360)	Hours – 7 days 2 (1-5)

Table 1. Demographics and characteristics of included cases

3.1. L- type CCBs and extrapyramidal symptoms

CCBs were implicated in extrapyramidal disorders in 14 cases of which 8 occurred in females. The median (Q1-Q3) age of affected individuals was 71 (63.5-75.5) years and ranged from 26 to 83 years. Eleven of these 14 cases (78.6%) occurred in older adults (≥60 years). Hypertension, diabetes, and arrhythmias were the common co-morbidities. Concomitant medications belonged to the class of angiotensin receptor blockers (n=3), beta blockers (n=3), sulfonylureas (n=3), diuretics (n=3) and benzodiazepines (n=3). Antipsychotics (chlorpromazine) were prescribed in one. Parkinsonism was the commonest phenotype observed (n=9) followed by dystonia (n=4). Two patients had more than one extrapyramidal phenotype. These included a case of dystonia and akathisia and another of Parkinsonian features along with dystonia (blepharospasm). One patient each developed akathisia and tardive akathisia. Eight cases were associated with the dihydropyridine (DHP) class of L-type CCBs of which amlodipine and nifedipine contributed to six and two cases respectively. Diltiazem and verapamil were involved in three cases each. The doses of amlodipine, nifedipine, verapamil, and diltiazem varied from 5-10 mg, 30-40 mg, 120-240 mg, and 90-360 mg, respectively. The time of onset of EPSs from the intake of CCBs varied from 1 day for dystonia to 8.5 years for tardive akathisia. Parkinsonism occurred after a median time of 90 (60-360) days of drug intake. Tremors (n=8), rigidity (n=6), postural instability (n=6), and dystonia (n=4) were the common individual symptoms. The case described as Parkinsonism by Graham DF had some features overlapping with acute dystonia and possibly with neuroleptic malignant syndrome (NMS).[20] Withdrawal of drug caused resolution of symptoms in 12 (85.7%) patients. Additional supportive measures such as dopaminergic drugs, anticholinergic drugs, or botulinum toxin were required in four cases. Symptoms improved after a median (Q1-Q3) time of 14 (4-75) days. Rechallenge done in three cases was followed by reemergence of EPS in all.[17][19][20] In one patient on concomitant neuroleptics, nifedipine caused drowsiness and a rechallenge of nifedipine was followed by the development of an oculogyric crisis that subsided with the discontinuation of nifedipine and neuroleptics.[16] A possibility of pharmacokinetic interaction by nifedipine leading to potentiation of EPS induced by neuroleptics was hypothesized (**Details in Table 2**).

Author and Year of publication	Patient age and sex	Culprit Drug	Comorbidities	Presenting symptom	Time of Onset	Final Diagnosis/ Phenotype	Concomitant drugs	Management	Response
Dressler D, 2013	72 years, male	Amlodipine, dose: not mentioned	Hypertension, Skin pseudo lymphoma 7 years back, Prostatic cancer	Severe and painful muscle cramps in the neck, involuntary eyelid closures, restlessness, difficulty in sitting still, breathing irregularity, anxiety, and lumbar back pain for 1.5 years	4 weeks	Dystonia, and akathisia	Not mentioned	Withdrawal of amlodipine	No improvement till 3 months of follow-up
Dressler D, 2013	70 years, female	Amlodipine, dose: not mentioned	Hypertension, Osteoporosis, Glaucoma	Low and compressed voice, swallowing difficulty, bruxism, muscular neck pain (cervical and pharyngo-laryngeal dystonia), involuntary eyelid closures (blepharospasm), breathing difficulties, depression, anxiety, reduced appetite for 1.5 years	8 weeks	Dystonia	Not mentioned	Withdrawal of amlodipine and botulinum toxin administration	No improvement after withdrawal of amlodipine. Botulinum toxin reduced cervical, mandibular, ocular, and facial symptoms. No remission till 9 months of follow-up.
Hsieh MT et al, 2017	57 years, female	Amlodipine 5mg/day	Hypertension, Type 2 diabetes mellitus, hyperlipidemia, Hyperthyroidism followed by thyroidectomy	Insomnia and bilateral lower limb restlessness for 1.5 years. Other symptoms: Depression, insomnia, memory impairment. Akathisia developed before antidepressants	8.5 years	Tardive akathisia	Olmesartan, atorvastatin, metformin, glyburide, thyroxine,	Withdrawal of amlodipine and replacement by bisoprolol. Addition of escitalopram, clonazepam, and zaleplon.	Improvement in depressive symptoms with escitalopram. Improvement in akathisia on a 3-month follow-up.
Teive HAG et al, 2002	83 years, female	Amlodipine 10mg/day	Hypertension, Osteoporosis, Depression,	Progressive gait disorder, bradykinesia,	2 months	Parkinsonism	Vitamin E, bromazepam, paroxetine,	Withdrawal of amlodipine	Motor functions improved within 30 days and mild

Author and Year of publication	Patient age and sex	Culprit Drug	Comorbidities	Presenting symptom	Time of Onset	Final Diagnosis/ Phenotype	Concomitant drugs	Management	Response
			Vestibular syndrome (light-headedness)	tremor, and frequent falls			omeprazole, selegiline		bradykinesia persisted at 12 months
Kaur U, 2018	74 years, female and 74 years, female (same patient)	Nifedipine 20mg two times a day	Hypertension, SIADH, Vitamin D deficiency	Tremors of bilateral upper and lower limbs, a tendency to fall, difficulty in walking within 1 day of nifedipine initiation, associated with low serum sodium levels	1 day	De Melo Souza syndrome (Parkinsonism)	Telmisartan, propranolol, amitriptyline, tolvaptan	Amitriptyline discontinued because of hyponatremia. Dose of propranolol increased to 80mg/day and nifedipine discontinued	Complete disappearance of tremors after nifedipine withdrawal. No improvement with propranolol.
		Amlodipine 5mg/day	Hypertension, SIADH, Vitamin D deficiency	Tremulousness of bilateral upper and lower limbs, a tendency to fall and features of depression	10 days	De Melo Souza syndrome (Parkinsonism)	Telmisartan, metoprolol, tolvaptan, clonazepam (as needed), paracetamol (as needed)	Amlodipine was stopped, telmisartan dose increased to 80mg/day, and propranolol and amitriptyline were added	Yes
Sempere AP et al, 1995	68 years, female	Amlodipine 10mg/day	Hypertension	Resting tremor in left hand, progressive bradykinesia, rigidity, hypomimia, slowness and mild postural instability	3 months	Parkinsonism	None	Withdrawal of amlodipine	Improvement in symptoms at 4-month follow-up
García-Albea E et al, 1993	55 years, male	Verapamil 240mg/day	Tachyarrhythmia	Resting and postural tremors in hand, axial rigidity, difficulty in speaking and walking, slowness, reduced arm swing	3 years	Parkinsonism	None	Withdrawal of verapamil. Levodopa/carbidopa (500mg/125mg daily), trihexyphenidyl 15 mg/day, propranolol added.	No improvement with levodopa/carbidopa or trihexyphenidyl. Postural tremor improved moderately with propranolol. Significant improvement in motor symptoms after verapamil

Author and Year of publication	Patient age and sex	Culprit Drug	Comorbidities	Presenting symptom	Time of Onset	Final Diagnosis/ Phenotype	Concomitant drugs	Management	Response
									withdrawal. Only mild tremors and minimal slowness in the left limb were present at 3 months of follow-up.
Padrell MD, 1995	70 years, female	Verapamil 120mg/day	Type 2 diabetes mellitus, Hypertension, Arrhythmia, Anxiety	Resting and postural tremors	4 months	Parkinsonism	Digoxin, amiodarone, insulin, occasional lorazepam	Verapamil replaced with doxazosin	Significant improvement over 2 months and complete resolution at 1 year
Padrell MD, 1995	79 years, female	Verapamil 120mg/day	Hypertension	Rigidity, bradykinesia, cogwheel phenomenon, mask-like facies, depression	2 years	Parkinsonism	None	Withdrawal of Verapamil	Full improvement in symptoms
Singh I, 1987	26 years, male	Nifedipine 10mg three times a day	Psychosis, Infantile autism, Anxiety, Hypertension	Drowsiness occurred within seven days of nifedipine administration, oculogyric crisis occurred during nifedipine re-administration	1 day of nifedipine re-administration	Oculogyric crisis (Dystonia)	Chlorpromazine, clopenthixol	Withdrawal of nifedipine for drowsiness. Both nifedipine and neuroleptics were stopped for the oculogyric crisis. Procyclidine was given for oculogyric crisis. Chlorpromazine was later continued, and captopril was added for hypertension	Drowsiness improved after nifedipine withdrawal. Oculogyric crisis improved with the withdrawal of both nifedipine and neuroleptics. No response with procyclidine.
Jacobs MB, 1983	62 years, male	Diltiazem 30 mg three times a day	Type 2 diabetes mellitus, Hypertension, Aortic stenosis, Angina pectoris, Congestive heart failure, Chronic obstructive pulmonary disease, Renal insufficiency	Frequent changing of posture, sitting, lying, standing, and pacing.	4 days	Akathisia	Digoxin, furosemide, metolazone, hydralazine, tolazamide, theophylline	Diphenhydramine and oxazepam were given for sedation and diltiazem was stopped	No improvement with diphenhydramine and oxazepam. Improvement occurred after diltiazem removal

Author and Year of publication	Patient age and sex	Culprit Drug	Comorbidities	Presenting symptom	Time of Onset	Final Diagnosis/ Phenotype	Concomitant drugs	Management	Response
Graham DF, 1994	76 years, male	Diltiazem 30mg three times a day	Ischemic heart disease, Type 2 diabetes mellitus, Osteoarthritis, Trigeminal neuralgia	Fever (axillary temperature 38.4^{0}C, titubation, resting tremor of upper limbs, neck rigidity, blepharospasm, reduced responsiveness, cogwheel rigidity of all four limbs, creatine kinase elevated (774 U/L, upper limit: 250 U/L)	12 months	Parkinsonism and dystonia	Metoprolol, furosemide, gliclazide, piroxicam, carbamazepine	All medications were stopped	Improvement in awareness and Parkinsonian features
Dick RS et al, 1989	77 years, male	Diltiazem 90mg four times a day	Coronary artery disease, Complex ventricular ectopy, Hypertension, Sick sinus syndrome, Recurrent pulmonary edema, Paroxysmal atrial flutter	Cogwheel rigidity in all four limbs, slow resting tremor of right upper limb, stooped posture, short shuffling steps, difficulty in walking	3 months	Parkinsonism	Digoxin, furosemide, procainamide, captopril, cyclandelate, hydralazine	Levodopa/carbidopa (100mg/25mg) three times a day and discontinuation of diltiazem over 2 weeks	Significant and gradual improvement in neurologic symptoms with persistence of slight cogwheel rigidity. No response to levodopa challenge.

Table 2. Cases of extrapyramidal disorders associated with L-type calcium channel blockers

Abbreviations: *CCB: Calcium channel blocker, NA: not applicable, SIADH: Syndrome of inappropriate ant-diuretic hormone secretion*

3.2. L-type CCBs and delirium or psychosis

Six cases of psychosis, three cases of delirium, and one case of mania were reported with L-type CCBs. Six of these patients were males. The median (Q1-Q3) age of affected patients was 66 (62-82) years, and the range varied from 24 to 85 years. Seven of these nine cases (77.8%) occurred in older patients of 60 years and above. Angina was the commonest co-morbidity (n=5) followed by hypertension (n=3). Nitrates (n=4) and beta blockers (n=2) were the common medications concomitantly taken by the patients. Of these nine cases, the presenting phenotype overlapped with both delirium and psychosis in one[21]. The time of onset of symptoms varied from hours to 7 days. Among the culprit drugs, nifedipine and diltiazem were involved in three and two cases respectively. In two cases, diltiazem interaction with other drugs was suspected as a cause of delirium or psychosis[22][23]. These included interaction with lithium in one and with fentanyl in another. In the latter, diltiazem was thought to have provoked delirium by inhibiting the metabolism of fentanyl and causing fentanyl toxicity. The doses of nifedipine, diltiazem, verapamil, and amlodipine in these cases were 10-30 mg (range), 30-180 mg (range), 320 mg, and 10 mg respectively. Delusions (n=4), agitation (n=3), hyperactivity (n=2), irritability (n=2), and hallucinations (n=2) were the common individual symptoms. The culprit CCB was removed in eight cases and was successful in inducing remission in all patients. Fentanyl was removed in the case where diltiazem was involved in pharmacokinetic enhancement of fentanyl and improvement happened within hours. Additional drugs such as antipsychotics were required in two cases.[22] Following CCB discontinuation, improvement time varied from hours to 21 days with a median time of 2[1][2][3][4] days. Rechallenge done in four cases caused the reappearance of symptoms in two (**Details in Table 3**).

Author and Year of publication	Patient age and sex	Culprit Drug	Comorbidities	Presenting symptom	Time of Onset	Final Diagnosis/ Phenotype	Concomitant drugs	Management	Response	Time of improvement
Kahn JK, 1986	84 years, male	Nifedipine 10mg/day	Angina	Psychosis, agitation, pacing, and restlessness	1 day	Psychosis	Transdermal nitroglycerine and sublingual nitroglycerine	Withdrawal of nifedipine	Yes, symptoms improved	1 day
Ahmad S, 1983	62 years, male	Nifedipine 10mg three times a day for 1 day	Angina	Abdominal cramps, diarrhoea irritability, inability to sit still, feeling of panic, agitation, tremulousness, depression	2 hours	Psychosis	No other drug was given	Withdrawal of nifedipine	Yes, symptoms improved	2 days
Dikici S, 1985	63 years, male	Amlodipine 10mg/day	Hypertension, Stroke (lacunar infarct in right internal capsule)	3 to 4 episodes of agitation and sleepiness, delirium	3 to 4 hours	Delirium	Ramipril, hydrochlorothiazide, aspirin	Amlodipine replaced with doxazosin	Yes, complete improvement in symptoms	5 – 6 hours
Jacobsen FM, 1987	24 years, female	Verapamil 320mg/day	Bipolar disorder type 1, Substance abuse	Running tendencies, auditory, visual, and tactile hallucinations, screaming	On the day of taking the 320mg dose and within 7 days of the 80mg dose	Delirium (Psychosis)	-	Verapamil discontinued and intramuscular chlorpromazine given. After the verapamil rechallenge was positive, the dose was reduced to 160 mg/day and amitriptyline added	Improved and remained in remission for 6 months	Not mentioned
Franklin GS, 1982	82 years, male	Nifedipine 10mg twice a day	Angina, Mild anemia, Left temporal lesion	Dementia, disorientation, delusions of wife being replaced by a young woman (Capgras Syndrome)	7 days	Delusions (Psychosis)	Propranolol, Isosorbide dinitrate, nitroglycerine for 4 years	Withdrawal of nifedipine and addition of haloperidol	Delusions improved	3 weeks
Levin TT et al, 2010	85 years, male	Diltiazem-fentanyl interaction	Non-small cell lung cancer, Treated carcinoma prostate, Benign prostatic	Hypoactive delirium-somnolence, bedbound with pinpoint pupils	3 days of diltiazem (2 weeks of fentanyl)	Delirium	Intravenous fentanyl 25 µg/hour for 2weeks, diltiazem	Fentanyl drip discontinued. Replaced with hydromorphone	Alert within hours of fentanyl drip discontinuation	Hours

Author and Year of publication	Patient age and sex	Culprit Drug	Comorbidities	Presenting symptom	Time of Onset	Final Diagnosis/ Phenotype	Concomitant drugs	Management	Response	Time of improvement
			hypertrophy, Chronic renal insufficiency, Gastroesophageal reflux disease, Supraventricular tachycardia							
Bushe CJ et al, 1988	72 years, female	Diltiazem 60mg three times a day	Hypertension, Unstable angina	Auditory hallucination, paranoid delusion, visual hallucination, and misinterpretation	2 days	Psychosis	Nil	Diltiazem replaced with nifedipine	Delusion improved within 3 days; mental state became normal in 7 days	3 days
Palat GK et al, 1984	56 years, male	Diltiazem 30mg four times a day	Stable angina	Irritability and hyperactivity followed after 8 weeks by labile mood, paranoid delusion, delusion of grandeur, pressure of speech	7 days	Mania	Propranolol, nitrate	Diltiazem withdrawn	Delusion, hyperactivity, and speech improved within 48 hours; threatening behavior improved within 7 days	2 days
Binder EF et al, 1991	66 years, female	Diltiazem 30mg three times a day, lithium carbonate 300mg four times a day	Hypothyroidism, Hypertension, Coronary artery disease, Degenerative joint disease, Bipolar affective disorder	Lethargy, confusion, delusions, lip smacking, ataxia, rigidity of all four limbs, cogwheeling of upper extremities	5 days	Psychosis	Nitroglycerin, estrogen, levothyroxine	Diltiazem removed. Lithium stopped for 2days	Yes, confusion and motor symptoms resolved	7 days

Table 3. Cases of delirium or psychosis associated with L-type calcium channel blockers

4. Discussion

Cav 1.2 and Cav1.3 of the Cav 1 family are the primary L-type calcium channels expressed on substantia nigra dopaminergic neurons. These channels are activated by high voltage and have long-lasting current[24]. The molecular pathways related to L-type calcium channel signaling are more complex than previously assumed. These channels play a role in pre-synaptic dopamine release, produce oxidative damage inside the dopaminergic neurons, and regulate the auto receptor (D2R) desensitization and dopamine-mediated excitotoxicity[7][25][26]. The association between L-type CCBs and extrapyramidal features is, however, scantily studied. The link between these drugs and their propensity to induce delirium and psychosis is uninvestigated. We recently noticed a case of delirium occurring twice in association with diltiazem use in an elderly female. Delirium manifested as mental confusion, irrelevant talking, and hallucinations and was complicated by the development of extrapyramidal features. With this background, the present review was conducted to interpret the evidence on the association of EPS, delirium, and psychosis with the L-type CCBs, to which older patients are commonly exposed for a long duration.

We observed that nearly 80% of cases of EPS with L-type CCBs occurred in older adults of 60 years and above and females were the victims in more than 50% of the cases. Pharmacokinetic interaction possibly increasing the levels of concomitant antipsychotic drug was observed in only one case. Parkinsonism was the most common phenotype and occurred after a median intake of CCBs for 3 months. The dihydropyridine (DHP) class of L-type CCBs was implicated in the majority and amlodipine was the commonest individual CCB involved. Most cases of EPS resolved with discontinuation of the CCB over a median time of 2 weeks.

Older adults were also the common victims of delirium or psychosis associated with L-type CCBs. Two-thirds of cases were reported in males and all cases occurred within a week of intake of the CCB. Nifedipine and diltiazem were the single most common culprit agents reported. Drug interactions were suspected in two cases. Symptoms resolved in all upon discontinuation of the drug over a median time of 2.5 days.

D2 receptor blockers such as antipsychotics and antiemetics including metoclopramide and levosulpiride are the well-known drugs implicated in EPS such as Parkinsonism and acute dystonia. The second most common class associated with EPS is voltage-gated CCBs[1][2] Among the latter, flunarizine and cinnarizine are classically linked with Parkinsonism to which older females are more susceptible. These drugs are antihistamines with additional T-type calcium channel blockade property[27] T-type calcium channels belonging to the Cav 3 family are primarily located on thalamocortical neurons and basal ganglia structures[3][4] These channels have high activation and deactivation rates implying the requirement of lower voltage for activation and a transient current flow. Among other drugs with voltage-gated calcium channel blocker property, valproate, pregabalin, and trimetazidine have also been linked with EPS such as Parkinsonism[28][29][30][31]

The mechanism of extrapyramidal features caused by CCBs lacks a clear understanding at present. Flunarizine reduces dopamine release as well as acts at post-synaptic dopamine receptors to reduce the effect of dopamine[32][33] These agents also interfere with the mitochondrial respiratory chain by competing with ubiquinone and by generating superoxides[34] Among the L-type CCBs, diltiazem has been shown to reduce the viability of dopaminergic cells in vitro[32]

Notwithstanding the risk of Parkinsonism with CCBs, larger epidemiologic electronic health record-based studies on the association between Parkinsonism and CCBs have generated disparate results. Reduced risk of Parkinsonism with the use of CCBs (DHPs and non-DHPs) was reflected in studies from Taiwan, the UK, and Denmark while no such protection was witnessed in studies enrolling patients from the United States and Germany[35][36][37][38][39][40]. A Pooled analysis of 2015 and very recently of 2024, based primarily on retrospective studies showed an overall 22-30% reduced risk of Parkinsonism with use of CCBs including DHPs and non-DHPs[41][42]. It is also possible that cases of EPS associated with CCBs are under-reported due to low awareness and the common presence of confounding polypharmacy in elderly patients.

There have been some claims about CCB-related neuroprotection, and the mechanism is hypothesized to be related to a reduction in intracellular calcium levels in the dopaminergic neurons of the substantia nigra (SN). Increased calcium inside the cells increases the vulnerability of these cells to calcium-induced mitochondrial dysfunction, oxidative stress, and degeneration[25][26]. Interestingly, however, the claims of prophylactic neuroprotection by CCBs observed in some retrospective studies were refuted in the randomized controlled settings where isradipine failed to slow the progression of Parkinson's disease[43].

The mechanistic explanation of psychosis or delirium with CCBs is obscure at present and needs clarity from future research. Voltage-gated calcium channels can modulate the pre-synaptic release of serotonin, acetylcholine, dopamine, and glutamate[5][44][45]. L-type calcium channels are located in the mesolimbic system and regulate the neuroplasticity and burst firing of dopaminergic neurons in the ventral tegmental area[46]. In a study, verapamil was shown to increase the basal and stimulated release of dopamine (DA). Whereas acute DA splurge can produce psychosis, prolonged CCB use causes DA receptor desensitization and induces EPS[47]. Interestingly, there are studies of successful treatment of schizophrenia and bipolar disorder with verapamil though the claims have been refuted in randomized controlled settings[48][49][50][51][52]. Likewise, CCBs have also been tried as experimental agents in patients with tardive dyskinesia with inconsistent outcomes[48][53][54].

Thus, the role of L-type calcium channels in the circuitry of the basal ganglia and mesolimbic system is more complex than imagined. Being cytochrome inhibitors, these drugs might also be involved in the pharmacokinetic enhancement of concomitantly administered dopamine modulators. The preventive or therapeutic disease-modifying role of CCBs in EPS, mood disorder, and schizophrenia needs scrutiny and validation from larger prospective studies and clinical trials. Comparative follow-up studies involving other classes of antihypertensives are also needed to assess the relative potential of each class to produce EPS or delirium.

4.1. Limitations

This review is an analysis of case reports and aims to describe the patients developing EPS and delirium with L-type CCBs. Retrospective studies have shown neutral to disease-modifying roles of L-type CCBs in Parkinsonism. Since the review is based on published cases, a strong possibility of reporting bias exists. The cases enrolled had patients on multiple other drugs, but the possibility of drug interactions existed in a few. The majority of the included case reports are old, and this might be because of the Weber effect which refers to a decline in the reporting of adverse drug reactions with older drugs. A case of drug toxicity was excluded as the review dealt with CCBs at therapeutic doses. N-type CCBs were not considered in the literature search. Unpublished literature, articles with unavailability of full text, and articles not in English language were excluded.

5. Conclusions

Older females were common victims of extrapyramidal disturbances associated with L-type CCBs while older males might be prone to delirium or psychosis. The majority of the cases of EPS and psychosis were associated with the dihydropyridine class and were reversible upon drug discontinuation. Understanding the complexities of calcium signaling inside the dopaminergic neurons of basal ganglia and the mesolimbic system will unravel the molecular pathways implicated in EPS and psychosis. Large prospective studies and randomized controlled trials are important to delineate the role of L-type CCBs in movement and mood disorders.

Statements and Declarations

Acknowledgments

UK and SSC acknowledge the IoE scheme of the Banaras Hindu University for general research support.

Funding

No funding was received for this study.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Ethics Statement

Not applicable.

References

1. a, b, c *Shin HW, Chung SJ. Drug-induced parkinsonism. J Clin Neurol. 2012 Mar;8(1):15–21.*
2. a, b, c, d *Teive HAG, Troiano AR, Germiniani FMB, Werneck LC. Flunarizine and cinnarizine-induced parkinsonism: a historical and clinical analysis. Parkinsonism Relat Disord. 2004 Jan;10(4):243–5.*

3. [a], [b], [c] Ortner NJ. Voltage-Gated Ca2+ Channels in Dopaminergic Substantia Nigra Neurons: Therapeutic Targets for Neuroprotection in Parkinson's Disease? Front Synaptic Neurosci. 2021 Feb 26;13.
4. [a], [b], [c] Matthews LG, Puryear CB, Correia SS, Srinivasan S, Belfort GM, Pan M, et al. T-type calcium channels as therapeutic targets in essential tremor and Parkinson's disease. Ann Clin Transl Neurol. 2023 Apr 4;10(4):462–83.
5. [a], [b] Brimblecombe KR, Gracie CJ, Platt NJ, Cragg SJ. Gating of dopamine transmission by calcium and axonal N-, Q-, T- and L-type voltage-gated calcium channels differs between striatal domains. J Physiol. 2015 Feb 15;593(4):929–46.
6. [^] Lee BJ, Yang CH, Lee SY, Lee SH, Kim Y, Ho WK. Voltage-gated calcium channels contribute to spontaneous glutamate release directly via nanodomain coupling or indirectly via calmodulin. Prog Neurobiol. 2022 Jan;208:102182.
7. [a], [b] Borgkvist A, Mosharov EV, Sulzer D. Calcium currents regulate dopamine autoreceptors. Brain. 2014 Aug;137(Pt 8):2113–5.
8. [^] Surmeier DJ, Schumacker PT. Calcium, bioenergetics, and neuronal vulnerability in Parkinson's disease. J Biol Chem. 2013 Jan;288(15):10736–41.
9. [^] Chan CS, Guzman JN, Ilijic E, Mercer JN, Rick C, Tkatch T, et al. "Rejuvenation" protects neurons in mouse models of Parkinson's disease. Nature. 2007 Jan;447(7148):1081–6.
10. [^] Dressler D. Tardive dystonic syndrome induced by the calcium-channel blocker amlodipine. J Neural Transm (Vienna). 2014 Jan;121(4):367–9.
11. [^] Hsieh MT, Lin PY, Tsai CJ, Chang CC, Lee Y. Tardive akathisia related to the anti-hypertensive agent Sevikar-a case report. BMC Pharmacol Toxicol. 2017 Jan;18(1):41.
12. [^] Teive HAG, Germiniani FMB, Werneck LC. Parkinsonian syndrome induced by amlodipine: case report. Mov Disord. 2002 Jan;17(4):833–5.
13. [a], [b] Kaur U, Das P, Gambhir IS, Chakrabarti SS. L-type calcium channel blockers and a symptom complex mimicking de Melo-Souza's syndrome. Neurol Sci. 2019 Jan;40(5):1077–80.
14. [^] Sempere AP, Duarte J, Cabezas C, Coria F, Clavería LE. Parkinsonism induced by amlodipine. Mov Disord. 1995 Jan;10(1):115–6.
15. [^] García-Albea E, Jiménez-Jiménez FJ, Ayuso-Peralta L, Cabrera-Valdivia F, Vaquero A, Tejeiro J. Parkinsonism unmasked by verapamil. Clin Neuropharmacol. 1993 Jan;16(3):263–5.
16. [a], [b] Singh I. Prolonged oculogyric crisis on addition of nifedipine to neuroleptic medication regime. Br J Psychiatry. 1987 Jan;150:127–8.
17. [a], [b] Jacobs MB. Diltiazem and akathisia. Ann Intern Med. 1983 Jan;99(6):794–5.
18. [^] Padrell MD, Navarro M, Faura CC, Horga JF. Verapamil-induced parkinsonism. Am J Med. 1995 Jan;99(4):436.
19. [a], [b] Dick RS, Barold SS. Diltiazem-induced parkinsonism. Am J Med. 1989 Jan;87(1):95–6.
20. [a], [b], [c] Graham DF, Stewart-Wynne EG. Diltiazem-induced acute parkinsonism. Aust N Z J Med. 1994 Jan;24(1):70.
21. [^] Jacobsen FM, Sack DA, James SP. Delirium induced by verapamil. Am J Psychiatry. 1987 Feb;144(2):248.
22. [a], [b] Levin TT, Bakr MH, Nikolova T. Case report: delirium due to a diltiazem-fentanyl CYP3A4 drug interaction. Gen Hosp Psychiatry. 2010;32(6):648.e9-648.e10.
23. [^] Binder EF, Cayabyab L, Ritchie DJ, Birge SJ. Diltiazem-induced psychosis and a possible diltiazem-lithium interaction. Arch Intern Med. 1991 Jan;151(2):373–4.
24. [^] Correa BHM, Moreira CR, Hildebrand ME, Vieira LB. The Role of Voltage-Gated Calcium Channels in Basal Ganglia Neurodegenerative Disorders. Curr Neuropharmacol. 2023;21(2):183–201.
25. [a], [b] Surmeier DJ, Schumacker PT. Calcium, bioenergetics, and neuronal vulnerability in Parkinson's disease. J Biol Chem. 2013 Apr 12;288(15):10736–41.
26. [a], [b] Chan CS, Guzman JN, Ilijic E, Mercer JN, Rick C, Tkatch T, et al. "Rejuvenation" protects neurons in mouse models of Parkinson's disease. Nature. 2007 Jun 28;447(7148):1081–6.
27. [^] Chu MK, Wang SJ. Nomenclature for flunarizine, cinnarizine, and lomerizine. Cephalalgia. 2020 Mar 19;40(3):321–2.
28. [^] Dy AMB, Limjoco LLG, Jamora RDG. Trimetazidine-Induced Parkinsonism: A Systematic Review. Front Neurol. 2020;11:44.
29. [^] Ari BC, Domac FM, Kenangil GO. A Case of Pregabalin-Induced Parkinsonism. Neurol India. 2020;68(6):1469–71.
30. [^] Kaur U, Ojha B, Pathak BK, Singh A, Gambhir IS, Chakrabarti SS. Aripiprazole-induced Parkinsonism with pregabalin as a confounder. Acta Neurol Belg. 2021 Oct;121(5):1351–6.
31. [^] Brugger F, Bhatia KP, Besag FMC. Valproate-Associated Parkinsonism: A Critical Review of the Literature. CNS Drugs. 2016 Jan;30(6):527–40.
32. [a], [b] Mena MA, Garcia de Yébenes MJ, Tabernero C, Casarejos MJ, Pardo B, Garcia de Yébenes J. Effects of calcium antagonists on the dopamine system. Clin Neuropharmacol. 1995 Oct;18(5):410–26.

33. ^Belforte JE, Magariños-Azcone C, Armando I, Buño W, Pazo JH. Pharmacological involvement of the calcium channel blocker flunarizine in dopamine transmission at the striatum. Parkinsonism Relat Disord. 2001 Sep;8(1):33–40.
34. ^Veitch K, Hue L. Flunarizine and cinnarizine inhibit mitochondrial complexes I and II: possible implication for parkinsonism. Mol Pharmacol. 1994 Jan;45(1):158–63.
35. ^Simon KC, Gao X, Chen H, Schwarzschild MA, Ascherio A. Calcium channel blocker use and risk of Parkinson's disease. Mov Disord. 2010 Sep 15;25(12):1818–22.
36. ^Ton TGN, Heckbert SR, Longstreth WT, Rossing MA, Kukull WA, Franklin GM, et al. Calcium channel blockers and beta-blockers in relation to Parkinson's disease. Parkinsonism Relat Disord. 2007 Apr;13(3):165–9.
37. ^Warda A, Reese JP, Tanislav C, Kostev K. The association between antihypertensive therapy and the incidence of Parkinson's disease in patients followed in general practices in Germany. Int J Clin Pharmacol Ther. 2019 Oct;57(10):483–8.
38. ^Tseng YF, Lin HC, Chao JCJ, Hsu CY, Lin HL. Calcium Channel blockers are associated with reduced risk of Parkinson's disease in patients with hypertension: A population-based retrospective cohort study. J Neurol Sci. 2021 May 15;424:117412.
39. ^Becker C, Jick SS, Meier CR. Use of antihypertensives and the risk of Parkinson disease. Neurology. 2008 Apr 15;70(16 Pt 2):1438–44.
40. ^Pasternak B, Svanström H, Nielsen NM, Fugger L, Melbye M, Hviid A. Use of Calcium Channel Blockers and Parkinson's Disease. Am J Epidemiol [Internet]. 2012 Apr 1 [cited 2025 Jan 7];175(7):627–35. Available from: https://dx.doi.org/10.1093/aje/kwr362
41. ^Lang Y, Gong D, Fan Y. Calcium channel blocker use and risk of Parkinson's disease: a meta-analysis. Pharmacoepidemiol Drug Saf. 2015 Jun;24(6):559–66.
42. ^Lin J, Pang D, Li C, Ou R, Yu Y, Cui Y, et al. Calcium channel blockers and Parkinson's disease: a systematic review and meta-analysis. Ther Adv Neurol Disord. 2024 Jan 19;17.
43. ^Parkinson Study Group STEADY-PD III Investigators. Isradipine Versus Placebo in Early Parkinson Disease: A Randomized Trial. Ann Intern Med. 2020 May 5;172(9):591–8.
44. ^Lee BJ, Yang CH, Lee SY, Lee SH, Kim Y, Ho WK. Voltage-gated calcium channels contribute to spontaneous glutamate release directly via nanodomain coupling or indirectly via calmodulin. Prog Neurobiol. 2022 Jan;208:102182.
45. ^Giovannini F, Sher E, Webster R, Boot J, Lang B. Calcium channel subtypes contributing to acetylcholine release from normal, 4-aminopyridine-treated and myasthenic syndrome auto-antibodies-affected neuromuscular junctions. Br J Pharmacol. 2002 Aug;136(8):1135–45.
46. ^Nunes EJ, Addy NA. L-type calcium channel regulation of dopamine activity in the ventral tegmental area to nucleus accumbens pathway: Implications for substance use, mood disorders and co-morbidities. Neuropharmacology. 2023 Feb 15;224:109336.
47. ^Tsuda K, Tsuda S, Masuyama Y. Effects of calcium-antagonists on dopamine release in the central nervous system--possible interactions with D2-autoreceptors and guanosine triphosphate-binding proteins. Jpn Circ J. 1992 Mar;56(3):248–54.
48. a, b Reiter S, Adler L, Angrist B, Peselow E, Rotrosen J. Effects of verapamil on tardive dyskinesia and psychosis in schizophrenic patients. J Clin Psychiatry. 1989 Jan;50(1):26–7.
49. ^Bloom DM, Tourjman S V, Nair NP. Verapamil in refractory schizophrenia: a case report. Prog Neuropsychopharmacol Biol Psychiatry. 1987;11(2–3):185–8.
50. ^Price WA. Antipsychotic effects of verapamil in schizophrenia. Hillside J Clin Psychiatry. 1987;9(2):225–30.
51. ^Wisner KL, Peindl KS, Perel JM, Hanusa BH, Piontek CM, Baab S. Verapamil treatment for women with bipolar disorder. Biol Psychiatry. 2002 May 1;51(9):745–52.
52. ^Cipriani A, Saunders K, Attenburrow MJ, Stefaniak J, Panchal P, Stockton S, et al. A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development. Mol Psychiatry. 2016 Oct;21(10):1324–32.
53. ^Dinan TG, Capstick C. A pilot study of verapamil in the treatment of tardive dyskinesia. Human Psychopharmacology: Clinical and Experimental [Internet]. 1989 Mar 1 [cited 2025 Jan 7];4(1):55–8. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/hup.470040110
54. ^Essali A, Soares-Weiser K, Bergman H, Adams CE. Calcium channel blockers for antipsychotic-induced tardive dyskinesia. Cochrane Database Syst Rev. 2018 Mar 26;3(3):CD000206.

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.