# Comparative effectiveness of calcium channel blockers as adjuvant therapies to antipsychotics in people with SMI: An emulated trial in English primary care electronic health records

## Background

Blood pressure should be regularly monitored for all patients with severe mental illness, and GPs are incentivised to measure blood pressure as part of an annual physical health check [1]. First line treatment for hypertension in primary care consists of monotherapy with calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) or thiazide-like diuretics [2, 3].

CCBs inhibit calcium ions by binding to L-type long-acting voltage-gated calcium channels. Two forms of these calcium channels are expressed in the brain and all three classes of CCBs (dihydropyridines, phenylalkylamines, and benzothiazepines) have been shown to bind to these[4].

Several recent pilot Randomised Controlled Trials (RCTs) have investigated the role of CCBs as adjuncts to antipsychotic medications, however these have been short in duration and in a small number of patients, often limited to one or two specific antihypertensives and with mixed results [5-8]. Likewise, mendelian randomisation studies have found mixed results. Mendelian randomisation studies using genetic proxies for CCBs have not found any link with incidence of bipolar disorder or schizophrenia, and results for depression have been mixed[9-11].

Findings from observational studies are also inconsistent, due in part to different populations and comparator drugs. A self-controlled case series analysis found that reduced admissions during periods of CCB prescription in patient with severe mental illness[12]. Several observational studies compare CCBs to ARBs and ACE inhibitors. These drugs also act upon renin-angiotensin systems, of which there are two in the brain[4] and have been implicated in both development and symptom improvement of mental health conditions. A large study of US data found that CCBs were associated with less recurrence of schizophrenia and bipolar disorder than beta blockers or ARBs, while comparisons between CCBs and ACE inhibitors were less consistent[13]. In contrast, a recent target trial emulation compared ACE inhibitors, ARBs, beta-blockers and CCBs across 262 outcomes of interest, found a lower prevalence of schizophrenia and psychosis in those prescribed ARBs compared to CCBs or ACE inhibitors[14]. Finally, Boal et al found that CCBs may be associated with increased risk of mood disorders compared to ACE inhibitors and ARBs[15].

Differences in blood-brain barrier penetrance may mask the effect of individual CCBs on psychiatric symptom improvement. For example, a study in Denmark suggested that CCBs other than amlodipine might have a role in reducing the risk of Parkinson’s disease[16]. They hypothesised that amlodipine may be less effective due to its reduced ability to cross the blood-brain barrier. Two studies of CCBs in people with severe mental illness stratified results by individual CCBs. The first, a self-controlled case series of patients with schizophrenia, found that while lercanidipine, amlodipine and nifedipine were associated with decreased psychiatric hospitalisations, diltiazem and verapamil were not [17]. The second found that those prescribed CCBs other than amlodipine had a slightly reduced risk of subsequent hospitalisation for bipolar disorder, schizophrenia and other psychoses. However, the authors note that residual confounding could have affected these results. This, the lack of primary care data providing detailed routine data, and the requirement to have two CCB prescriptions two years apart means these results require replication[18].

## Study design

### Study question

Do patients with SMI currently prescribed antipsychotics and initiating blood-brain barrier penetrating (BBBP) dihydropyridine have fewer psychiatric admissions than those initiating amlodipine (a non-BBBP dihydropyridine)?

### Hypothesis

People initiating blood brain barrier penetrant CCBs in addition to treatment as normal will have fewer psychiatric admissions than those initiating non-blood brain barrier penetrant CCBs.

### Target trial framework

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|  | **Target trial** | **Emulated trial** |
| Inclusions | Adults (aged > 18 and <100 at study entry) with a diagnosis of SMI prior to entry and with at least 6 months of psychotropic medication (antipsychotic, lithium, sodium valproate or lamotrigine) use at a therapeutic dose with newly diagnosed hypertension for which an oral CCB is indicated. | Adults (aged >18 and <100 study entry) with a diagnosis of SMI recorded in their EHR with a first prescription for oral CCB monotherapy and with at least one prescription for psychotropic medication (antipsychotic, lithium, sodium valproate or lamotrigine) at a therapeutic dose in the 6 months prior to CCB prescription. |
| Exclusions | * Prior prescriptions of CCBs, ARBs or ACE-inhibitors with hypertension indication * Prescription of CCBs with no hypertension indication (injectable and topical forms of diltiazem and nimodipine) in the 3 months prior to study entry * Injectable antipsychotics in the 3 months prior to study entry * Contraindications to CCBs (heart failure) * Dementia, Raynaud’s or diabetes diagnosis | * Prior prescriptions of oral CCBs, ARBs or ACE-inhibitors with hypertension indication * Prescription of CCBs with no hypertension indication (injectable and topical forms of diltiazem and nimodipine) in the 3 months prior to study entry * Injectable antipsychotics in the 3 months prior to study entry or antipsychotics not at therapeutic dosea. * Contraindications to treatments can be assumed to be absent given they will be prescribed statins in clinical practice. * Dementia, Raynaud’s or diabetes diagnosis |
| Treatment strategies | 1. Initiate amlodipine [comparison arm] 2. Initiate BBBP dihydropyridine CCB | Same |
| Assignment procedure | Randomly assigned at baseline to treatment or comparison arms, but aware of their status. | Assigned at study entry to treatment or comparison arms based on the initiation of CCB monotherapy as recorded in their EHR, with randomisation emulated through controlling of confounders. |
| Recruitment period | Jan 2000 to December 2018. | Same. |
| Start of follow up | Randomisation which must occur within three months of diagnosis of hypertension. | CCB monotherapy initiation. |
| End of follow up | Outcome of interest (for time-to-event), loss to follow up, two years of follow up, or December 2019. | Outcome of interest (for time-to-event), death, end of EHR (for CPRD only), two years of follow up, or December 2019. |
| Outcome | 1. Mental health related hospitalisations composite measure 2. Psychiatric hospitalisation 3. Self-harm hospitalisation | Same. |
| Causal contrast of interest | Intention to treat effect. | Observational analogue of intention to treat effect. |
| Analyses | Hazard ratio. | Hazard ratio. |

a: Therapeutic dose will be determined for commonly prescribed antipsychotics as per [19]

### Sample size calculations

Using a type 1 error rate of 0.05, a type 2 error rate of 0.2 and assuming that the arms of the trial are balanced, 631 psychiatric hospitalisations would be required to find a significant effect for a relative hazard equal to or less than 0.8. Assuming a baseline event rate of 0.1 hospitalisations per patient per year in the unexposed group, and follow up of two years, 2,527 patients would be required in each arm. For an effect size of 0.9, 10,072 patients would be required.

### Exposures

This is a 2-arm TTE. Exposure in each arm will be the following first oral monotherapy prescriptions, as recorded in primary care:

* Comparator arm: Non-blood brain penetrant dihydropyridine CCB: amlodipine
* Active arm: Blood brain penetrant dihydropyridine CCB: felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine or nisoldipine.

### Outcomes

The primary outcome is a composite measure of mental health related (psychiatric or self-harm) hospitalisation. Secondary outcomes are: hospitalisation for self-harm, and psychiatric hospitalisation. All outcomes will be measured at 12-week, 6 month, 12 month and two years, with outcomes at one year being the primary time point.

#### Operationalising the outcome

* Psychiatric hospitalisation: First recorded diagnosis of a hospitalisation is an ICD-10 “F” code, or first code is a mental health symptom (R41, R44, R45, R46) or observation (Z00.4, Z03.2, Z13.3, Z73), with F as a secondary diagnosis. Planned and unplanned admissions included.
* Self-harm hospitalisation: First recorded diagnosis of a hospitalisation is an ICD-10 code for self-harm (Y10-34, X60-84, Y87.0), or an accident or injury admission with self-harm coded during admission.

### Controlling for confounding

The following confounders will be controlled for using adjustment of statistical models:

* Age at index
* Year at index
* Time between hypertension diagnosis and index. Where no hypertension diagnosis is recorded prior to antihypertensive prescription, this will be assumed to have occurred on the same day.
* CCB dose (Starting, maintenance or maximum)
* Sex
* Region (9 Office or National Statistics English regions)
* Ethnicity (Categorised as per ONS Census categories)
* SMI diagnosis (schizophrenia, bipolar disorder, other psychoses)
* Proxy of SMI severity:
  + Number of psychiatric admissions in the previous year
  + Time since SMI diagnosis/antipsychotic/bipolar disorder medication
  + Number of self-harm events in the previous year
* Cardiovascular disease diagnoses:
  + Myocardial infarction (ever recorded in GP or hospital records prior to index)
  + Congestive heart failure (ever recorded in GP or hospital records prior to index)
  + Cerebrovascular disease (ever recorded in GP or hospital records prior to index)
* BMI value (continuous)
* Most recent blood pressure reading (within 3 years prior to index)
* Prescription of antidepressants in 6 months prior to index
* Type of antipsychotic or mood stabiliser most recently prescribed
* Number of previous GP appointments in the six months prior to index
* Number of physical health and accident/injury hospital admissions in the one year prior to index
* Index of Multiple Deprivation quintiles

### Missing data

It is likely that missing data will be present for ethnicity in CPRD. Where this is the case missing data will be imputed using multiple imputation. An absence of data for all diagnoses will be assumed to denote an absence of diagnosis. Missing dosage will be imputed as the median dose for that drug. Missing BMI and blood pressure will be multiply imputed using within and between patient data.

### Analysis plan

Our primary analysis will use Cox regression to quantify the hazard ratio of outcomes between treatment arms. We will test for proportional hazards and where there is deviation from this assumption, we will calculate the hazard ratio at set time points. All analyses will be stratified by SMI diagnosis where numbers allow and a secondary analysis will restrict the cohort to those receiving antipsychotics.

### Sensitivity analyses

1. Use of inverse probability weighting or overlap weights to control for confounding:
   1. Known confounders and prognostic factors will be controlled for using inverse probability weighting (IPW) for average treatment effects or overlap weights using covariates at baseline. For IPW, factors related only to treatment arm designation will not be included.
2. Altering the exclusion criteria to improve sample size
   1. Given the specificity of the research question it is hypothesised that some arms of the trials may suffer from small numbers. This sensitivity analysis will therefore employ a less stringent requirement regarding previous anti-hypertensive use, excluding only those with anti-hypertensive use in the 6 months prior to initiation.
3. Per-protocol effect
   1. Per-protocol analysis to consider switching, adherence and discontinuation of statins

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