Do certain statins improve psychiatric symptoms in people with severe mental illness?

Attempting to pick apart mechanisms of action using electronic health records and target trial emulation

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INTRODUCTION

There are five different statins prescribed for high cholesterol in primary care in the UK. Others have hypothesised that their anti-inflammatory nature might drive psychiatric symptom improvement in people with severe mental illness (SMI: schizophrenia, bipolar disorder and other psychoses). However, randomised controlled trials, meta-analyses and observational studies have had mixed results. This may be because of the different biochemical properties of both statins and antipsychotics. We wanted to test whether we could use Electronic Health Records (EHRs) to investigate mechanisms of action.

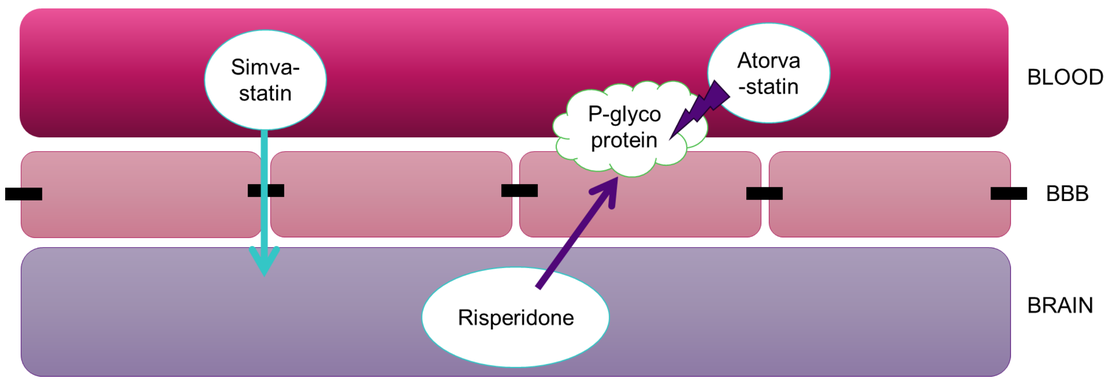
HYPOTHESES

In patients with SMI:

Statins that cross the BBB (simvastatin) will improve psychiatric symptoms compared to statins that don't (atorvastatin, pravastatin, rosuvastatin) due to their anti-inflammatory properties.

Statins that inhibit P-glycoprotein (simvastatin, atorvastatin) will improve psychiatric symptoms compared to those that don't (pravastatin) in people on antipsychotics which have affinity for P-glycoprotein (risperidone, aripiprazole, olanzapine)

Antipsychotics with affinity for P-glycoprotein (risperidone, aripiprazole, olanzapine) will improve psychiatric symptoms compared to those that don't have affinity (quetiapine) in people on statins which inhibit P-glycoprotein (simvastatin, atorvastatin)



METHODS

Study design: Target Trial Emulation of three hypothetical trials (Fig 1 and QR code) using CPRD (GP) and HES (hospital) records for England, 2000-2018.

Broad inclusions: SMI; age 18-100; on antipsychotic or mood stabilisers; with statin prescription; no injectable antipsychotics

Trial specific inclusions: QR code and Table 1.

Primary outcomes: 12-month psychiatric admissions

Confounders: Age, sex, year, time since SMI, time since dyslipidaemia, statin dose, region, ethnicity, SMI diagnosis, hypertension, myocardial infarction, heart failure, cerebrovascular disease, obesity, diabetes, cholesterol level, antidepressants, healthcare contact

Statistical analysis: Intention to treat (ITT) analysis using Cox regression with confounder adjustment and stratified by SMI diagnosis. Multiple imputation for missing data.

Secondary analysis: ITT negative binomial with confounder adjustment

Sensitivity: Inverse probability weighted Cox and per-protocol analysis (PPA).

Table 1: An example from the BBB trial: our hypothetical target trial and emulated trial

	Target trial	Emulated trial
Inclusions	Adults (>18 years 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 dyslipidaemia for which a statin is indicated.	Adults (>18 years at study entry) with a diagnosis of SMI recorded in their EHR with a first prescription for statins 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 statin prescription.
Exclusions	• Prior prescriptions of statins • Dyslipidaemia prior to study entry • Injectable antipsychotics in the 3 months prior to study entry • Contraindications to statins (hepatic impairment and myopathy)	• Prior prescriptions of statins • Injectable antipsychotics in the 3 months prior to study entry or antipsychotics not at therapeutic dose. • Contraindications to statins can be assumed to be absent given they will be prescribed statins in clinical practice.
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 statins as recorded in their EHR, with randomisation emulated through controlling of confounders.
Start of follow up	Randomisation which must occur within three months of diagnosis of dyslipidaemia.	Statin initiation.
End of follow up	Outcome of interest (for time-to-event), loss to follow up, three years of follow up, or Dec 2019.	Outcome of interest (for time-to-event), self-harm, death, end of EHR (for CPRD only), three years of follow up, or Dec 2019.

RESULTS

Of over 300,000 patients with SMI, 72,096 met our broad inclusion criteria. Patients were older than in our previous research with differences in key variables between study arms (Table 2).

BBB crossing statins: No significant difference in psychiatric hospitalisations or self-harm episodes at 3, 6, 12 or 14 months (Fig 1).

P-glycoprotein statins: Low number of patients on pravastatin (n=100, Table 2) meant the trial was under-powered. No significant differences in outcomes at any time point (Fig 2).

Table 2: Key characteristic by trial and trial arm

		BBB crossing statins		P-glycoprotein inhibiting statins		P-glycoprotein affinity antipsychotics	
Arm		**Doesn't cross**	**Crosses (active)**	**Doesn't inhibit**	**Inhibits (active)**	**No affinity**	**Affinity (active)**
n		6,703	12,330	100	5,981	2,645	6,753
Age at index (med [IQR])		56 [48-66]	57 [47-66]	54 [46-65]	54 [46-64	65 [54-76	66 [55-76]
Years on antipsychotics/mood stabilisers (med [IQR])		8 [3-14]	8 [3-13]	5 [2-9]	7 [3-12]	2 [0-10]	1 [0-9]
Cerebrovascular disease (%)		105 (1.6)	228 (1.9)	<5	99 (1.7)	100 (3.8)	213 (3.2)
Diabetes (%)		445 (6.6)	924 (7.5)	6 (6.0)	458 (7.7)	183 (6.9)	558 (8.3)
Resident in London (%)		1505 (22.5)	2598 (21.1)	35 (35.0)	1492 (25.0)	451 (17.1)	1531 (22.7)
Years since dyslipidaemia	Med [IQR]	3 [0-7]	2 [0-5]	0 [0-2]	2 [0-5]	5 [2-10]	5 [1-10]
	Imputed as 0	753 (11.2)	1259 (10.2)	27 (27.0)	548 (9.2)	385 (14.6)	1109 (16.4)

P-glycoprotein antipsychotics: No significant difference at any time point in primary analysis (Fig 3), but lower psychiatric admissions in people with a diagnosis of other psychoses, lower psychiatric admissions in the negative binomial model and lower self-harm in the PPA (Fig 4).

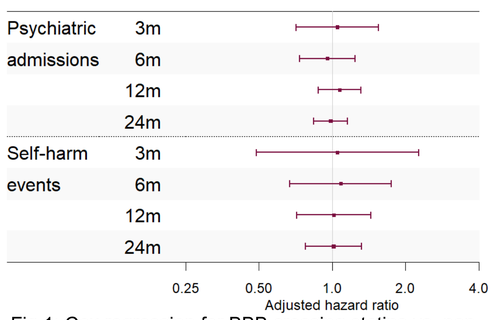


Fig 1: Cox regression for BBB crossing statins vs. non-crossing statins

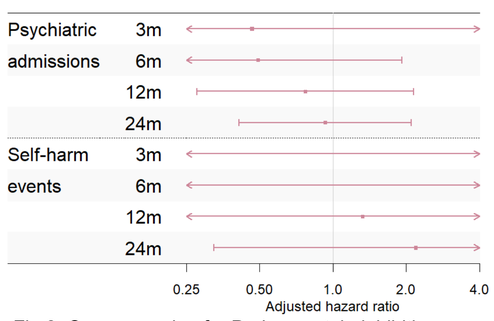


Fig 2: Cox regression for P-glycoprotein inhibiting statins vs. inhibiting statins

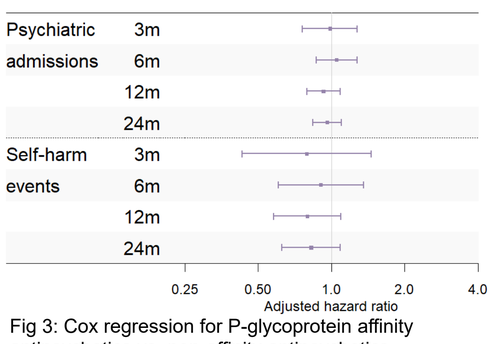


Fig 3: Cox regression for P-glycoprotein affinity antipsychotics vs. non-affinity antipsychotics

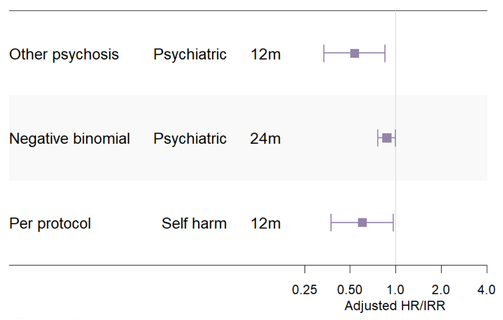


Fig 4: Secondary/sensitivity analyses with significant findings

CONCLUSIONS

- Target trial emulation is useful for improving the rigour of electronic health record studies
- But produces a very specific population and requires very large numbers
- Our outcomes were limited to EHRs so low sensitivity
- Our population was comparatively old – raises questions of generalisability
- **BBB penetrance** doesn't appear to drive symptom improvement
- Weak evidence for P-glycoprotein theory, but:
  - **P-glycoprotein statins**: Under-powered
  - **P-glycoprotein antipsychotics**: Despite previous research showing these antipsychotics are equivalent, the observed differences could be due to differing antipsychotic effectiveness

Full protocol, code lists, R scripts, a copy of this poster and a pre-print manuscript are available on my GitHub page via this QR code:

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