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Physicians' prescribing preferences were a potential instrument for patients' actual prescriptions of antidepressants☆

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Abstract

Objectives: To investigate whether physicians' prescribing preferences were valid instrumental variables for the antidepressant prescriptions they issued to their patients.

Study Design and Setting: We investigated whether physicians' previous prescriptions of (1) tricyclic antidepressants (TCAs) vs. selective serotonin reuptake inhibitors (SSRIs) and (2) paroxetine vs. other SSRIs were valid instruments. We investigated whether the instrumental variable assumptions are likely to hold and whether TCAs (vs. SSRIs) were associated with hospital admission for self-harm or death by suicide using both conventional and instrumental variable regressions. The setting for the study was general practices in the United Kingdom.

Results: Prior prescriptions were strongly associated with actual prescriptions: physicians who previously prescribed TCAs were 14.9 percentage points (95% confidence interval [CI], 14.4, 15.4) more likely to prescribe TCAs, and those who previously prescribed paroxetine were 27.7 percentage points (95% CI, 26.7, 28.8) more likely to prescribe paroxetine, to their next patient. Physicians' previous prescriptions were less strongly associated with patients' baseline characteristics than actual prescriptions. We found no evidence that the estimated association of TCAs with self-harm/suicide using instrumental variable regression differed from conventional regression estimates (P-value = 0.45).

Conclusion: The main instrumental variable assumptions held, suggesting that physicians' prescribing preferences are valid instruments for evaluating the short-term effects of antidepressants.

Keywords: Instrumental variables; Clinical Practice Research Datalink (CPRD); Physicians' prescribing preferences; Confounding by indication; Causality; Translational epidemiology

1. Introduction

In observational research, confounding by indication can bias estimates of drug treatment effects on outcomes that are associated with the indications for treatment [1,2]. Standard statistical approaches to deal with this adjust associations for observed covariates [3]. However, many confounders are difficult or impossible to measure [4], and a number of observational associations have been contradicted by subsequent randomized controlled trials [5,6]. This has been ascribed to unmeasured or residual confounding by indication. Observational studies can also suffer from reverse causation and protopathic biases, in which preclinical symptoms of diseases affect prescribing decisions or the ability of patients to comply with a treatment regime [7,8].

One approach to address these sources of bias is instrumental variable analysis [9−16]. This uses naturally occurring

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What is new?

- Physicians' prior antidepressant prescribing patterns were strongly associated with their subsequent prescriptions.
- Physicians' prior antidepressant prescriptions were less strongly associated with the observable baseline characteristics of patients (potential confounders) than the actual prescriptions.
- Multiple prior prescriptions were more strongly associated with the actual prescription than a single prior prescription.
- Prior prescriptions can potentially be used to estimate treatment effects using observational data in the presence of unmeasured confounding by indication when investigating the short-term effects of antidepressants.
- There was no evidence that the association of TCAs vs. SSRIs with self-harm/death by suicide was affected by residual confounding because the results from conventional ordinary least squares regression were similar to the instrumental variable results. However, this may be because of the imprecision of the instrumental variable results.

variation in likelihood of prescription, ''the instrumental variable'' or ''instrument,'' that is associated with the actual prescription but, unlike the actual prescription, is not associated with observed and unobserved confounding factors. Variation in drug prescribing associated with the instruments can provide unconfounded estimates of causal relationships between being prescribed a drug and an outcome, provided a set of assumptions are met (see Box 1).

Brookhart et al. [17] proposed that physicians' preferences for medications could be an instrumental variable for the actual prescriptions their patients received. In most observational datasets, it is not possible to directly measure physicians' prescribing preferences; therefore, Brookhart et al. argued that the prescriptions issued by physicians to their previous patients could be used as a proxy of their preferences, and hence that prior prescriptions could be used as a surrogate instrument. Brookhart et al. used this concept to estimate the effects of cyclooxygenase-2 selective inhibitors vs. traditional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) on upper gastrointestinal complications [17]. They found that physicians' prior prescriptions predicted the actual prescriptions received and that associations of potential confounders with physicians' prior prescriptions were weaker than with the actual prescriptions. Furthermore, conventional multivariate regression methods found little difference in rates of upper gastrointestinal complications by actual prescription, whereas an instrumental variable analysis, using physicians' prior prescriptions as a surrogate instrument for actual prescriptions, found evidence that patients prescribed cyclooxygenase-2 selective inhibitors had fewer upper gastrointestinal complications, in line with randomized controlled trials [18−21]. The methods have been developed in subsequent studies [15,22−29].

There has previously been concern about whether selective serotonin reuptake inhibitors (SSRIs), in particular paroxetine, cause suicide-related serious adverse events [30−33]. In this study, we evaluated physicians' prescribing preferences as an instrument for patients' prescriptions of tricyclic antidepressants (TCAs) vs. SSRIs and paroxetine vs. SSRIs, using data from the United Kingdom's Clinical Practice Research Datalink (formerly the General Practice Research Database). To evaluate the three assumptions underpinning instrumental variable analysis, we present associations of prior prescriptions (the surrogate instrument) with actual prescription and compare the strength of associations of potential confounders with prior prescriptions to that of the actual prescriptions received. We also developed the methodology by evaluating the properties of alternative instruments based on a greater number of prior prescriptions.

2. Methods

The Clinical Practice Research Datalink (www.cprd.com) is an administrative and clinical database containing data on over 11 million patients (4.5 million of whom are currently registered) from over 600 general practices across Britain [34]. Registered patients are representative of Britain's demography in terms of age, sex, and geographical distribution [35]. Data are validated, audited, quality checked [36,37], and have been used in over 800 peer-reviewed articles [36,38−41].

2.1. Study participants

We identified all patients ever registered with a practice contributing to the Clinical Practice Research Datalink before June 20, 2011, and whose records indicated that they had been prescribed an SSRI or a TCA (Appendix at www.jclinepi.com) while registered with the practice. We extracted data relating to all the antidepressant prescriptions given to these patients. We excluded prescription records if they occurred before the patients were registered at the practice, were missing a prescription date, or occurred after the patient's registration end. We kept the first prescription issued to each of the remaining patients. Of these, we excluded (1) patients first prescribed an antidepressant within 12 months of joining the practice as these may have been repeat prescriptions for medicines first prescribed by their previous general practitioner; (2)