[Latimer]

This online supplement is designed to be read as supplementary notes to the corresponding sections in the paper.

Study setting

In Québec, for the population that is covered by a public prescription drug plan, modest deductibles and co-pays may be applied depending on the insured's income level. There is no maximum to the amount that the government may reimburse. As a result, all prescriptions filled are recorded.

Analytic population

Using unique patient identifiers included in all claims, pharmaceutical claims data were linked with hospitalization records (provincial Med-Echo data base, which contains detailed records of each hospitalization in the province of Québec) as well as with medical claims (data base held by the *Régie d'Assurance-Maladie du Québec*, or RAMQ – Québec Health Insurance Board), which records almost all medical services provided in the province. Data cleaning procedures (checks on prescription duration and consistency between cost, quantity and duration fields on prescription records) eliminated 467 individuals who had at least one diagnosis of schizophrenia. No diagnosis is recorded on claims for pharmaceuticals, so that only hospitalization and physician claims records could be used to identify people with schizophrenia.

Defining a high dose

Many published sources of CPZE conversions exist based on receptor occupancy studies of dopamine (D2) as well as therapeutic responses and clinical data (1-4). An

average of CPZE conversion factors for each drug from consensus data in the literature
(3, 5-8) was used as the CPZE for each antipsychotic included in this study.

Second-generation antipsychotics (SGAs) generally share a lower binding affinity
for D2 receptors, as well as an ability to act on serotonergic receptors (4, 9).
Accordingly, a 1000 mg CPZE threshold for these drugs would tend to correspond to a
relatively higher dose than for first-generation antipsychotics (FGAs) (7, 10). In our data,
a 1000 mg CPZE threshold for FGAs corresponds to the 85th percentile of the distribution
of average daily CPZE doses of patients taking FGAs only that we observed in 2004. For
patients taking SGAs alone, or in combination with oral FGAs, we defined a high dose as
being above the 85th percentile of the distribution of doses in those situations, or 808 mg
CPZE. As a significant proportion of daily dosages for long-acting injectable
antipsychotics, or depot medications (mostly FGAs at the time), exceeded 1000 CPZEs,
we used, conservatively, a similar procedure to define a high dose for these drugs : the
85th percentile of dosages for these drugs alone or in combination corresponds to 1556
mg CPZE.

Patient characteristics.

Sex and date of birth were obtained from a linked patient characteristics dataset.
Age in 2004 was represented categorically, in order to take into account the non-linear
relation between antipsychotic dosage and its effects as age varies (11).

In addition, we used a linked file to identify the welfare/disability benefits status
of each patient at each point in time during the year. Patient welfare/disability benefits
status during 2004 was coded as a categorical variable: always receiving benefits and
below 65 years old, sometimes or never and below 65 years old, above 65 years old.

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Patients receiving welfare benefits the entire year are likely to be more severely ill than those receiving benefits a smaller proportion of the year and who are under 65. Those over 65 are all covered by the plan for seniors, so being on this plan carries no information about illness severity.

We also tested, as a measure of illness severity, the number of hospital days in the previous year. This variable, however, did not contribute to the explanatory power of the models, and was discarded.

Physician characteristics

Physician specialty was coded as either Psychiatrist or General Practitioner (GP), as these were the only specialties that were identified as being sole prescribers of psychotropic drugs to patients with schizophrenia. Physician year of graduation was coded as a binary value: before 1980 or during/after 1980. Physician school of graduation was also represented as a set of binary variables, one for each of four universities within the province of Quebec, one for universities outside of the province of Quebec and one indicating that university is unknown. Specialty and year of graduation have been associated with prescribing of high dose antipsychotics or antipsychotic polypharmacy (12). Physician school of graduation has been associated with prescribing practices in Québec (13).

Linking of patients to hospitals

We used ICD-9 codes 290.X-319.X: psychoses, neurotic disorders, and other nonpsychotic mental disorders to designate a principal psychiatric diagnosis. Of the 2,191 physicians in the data set, 524 were assigned to a hospital. Construction of the analytic data sets is summarized in Figure S1.

Classification of hospitals by urbanicity and psychiatric/general status

Hospitals were classified as urban if they were in Montreal, Québec City, Laval or Montérégie (most of the hospital capacity in Montérégie serves patients in the Montreal metropolitan area). Five hospitals were identified (based on location and patient volume) as psychiatric, located in Montreal, Québec City and the city of Gatineau.

Data analysis

In order for the generalized linear and latent mixed model (GLLAMM) to be estimable, we needed to remove from our sample patients (and their physician) who were the sole patient of a physician, as well as physicians who were the sole physician linked to a hospital. As there were 786 such patient-physician and physician-hospital pairs, this left us with 11,364 patients, 922 physicians and 54 hospitals.

We calculated the proportion of patients on a high dose for each physician by summing the number of patients that they had on a high dose and dividing by the number of patients for whom they were the sole prescriber of antipsychotic medications. The expected proportion of patients on a high dose was then calculated for each physician by taking the average of each of their patients' predicted probability of being on a high dose, where the predicted probability of being on a high dose was generated from a logistic regression using the following patient characteristics as adjusters: male sex, age, whether physician prescribes clozapine, and welfare status. The adjusted proportion was then calculated for each physician by taking the difference between the observed and expected proportion on a high dose for that physician and adding the average proportion of patients on a high dose across the dataset. The results are illustrated in Figure S2.

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Analogously, the observed proportion of patients on a high dose was calculated for each of the 60 hospitals in the dataset by summing the number of patients on a high dose in a given hospital and dividing by the total number of patients assigned to that hospital. The expected proportion of patients on a high dose was calculated for each hospital by taking the average across each patient's predicted probability of being on a high dose in a given hospital. The adjusted proportion was then calculated for each hospital by taking the difference between the observed and expected proportion on a high dose for that hospital and adding the average proportion of patients on a high dose across the dataset. The observed and adjusted proportions of patients on a high dose were stratified by hospital size. The results are illustrated in Figure S3.

Figure S1. Construction of analytic samples

21,535 patients with schizophrenia taking antipsychotics in 2004

12,150 patients taking antipsychotics for 11 months or more

11,364 patients whose 922 physicians prescribed antipsychotics to more than one patient and who were not the sole physician linked to one of 55 hospitals

Subset that can be used in GLLAMM regression model

2,191 physicians who prescribed to one or more of 12,150 patients

610 physicians without a single patient for whom they are sole prescriber

1,581 physicians with one or more patients for whom they are sole prescriber

7,430 patients linked to a single prescribing physician

4,720 patients NOT linkable to a single prescribing physician (but whose prescribing physicians may be at same hospital)

7,810 patients linked to a hospital

Any hospitalization their patients experience cannot be associated with a particular physician: They cannot be linked to a hospital
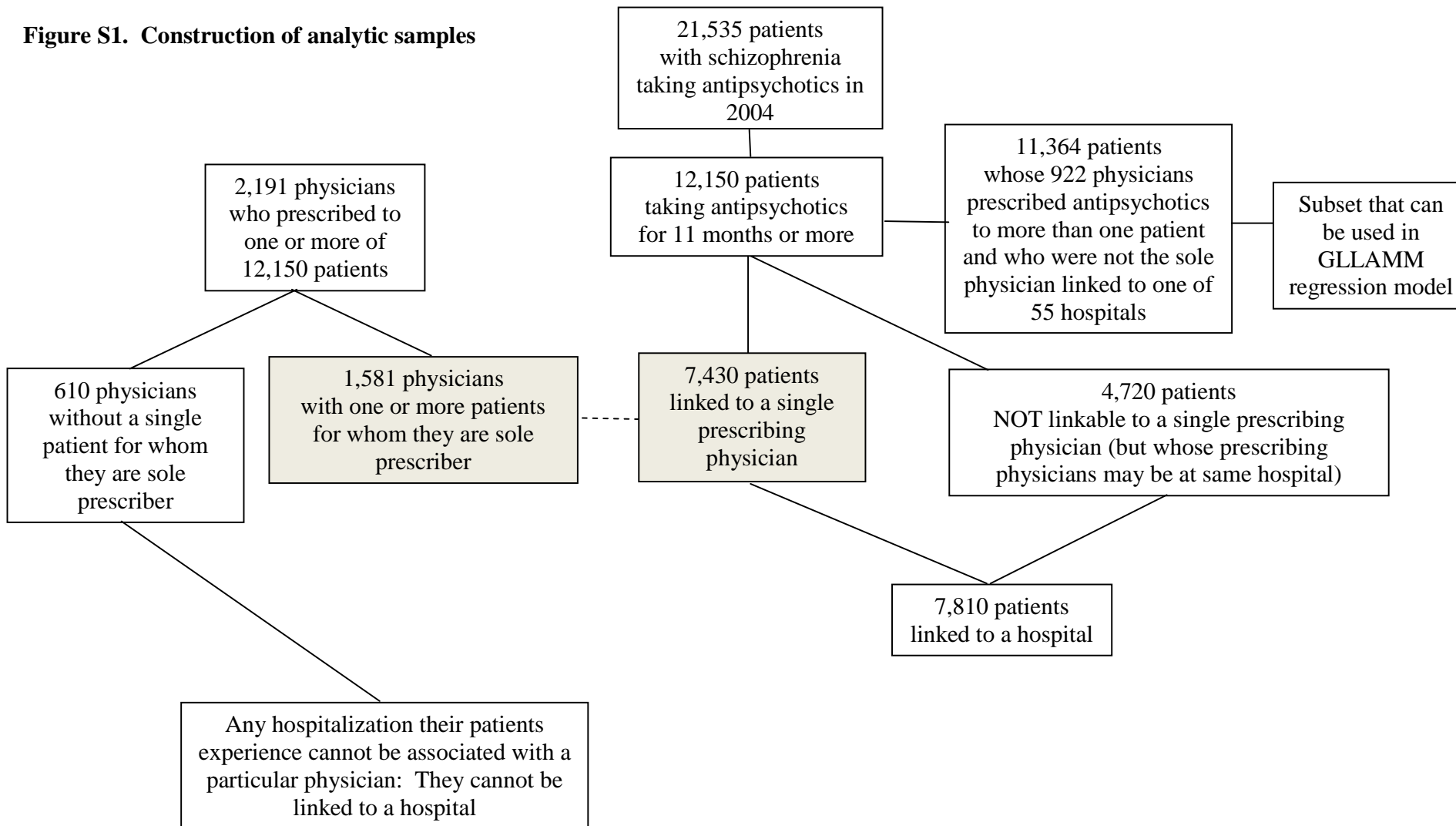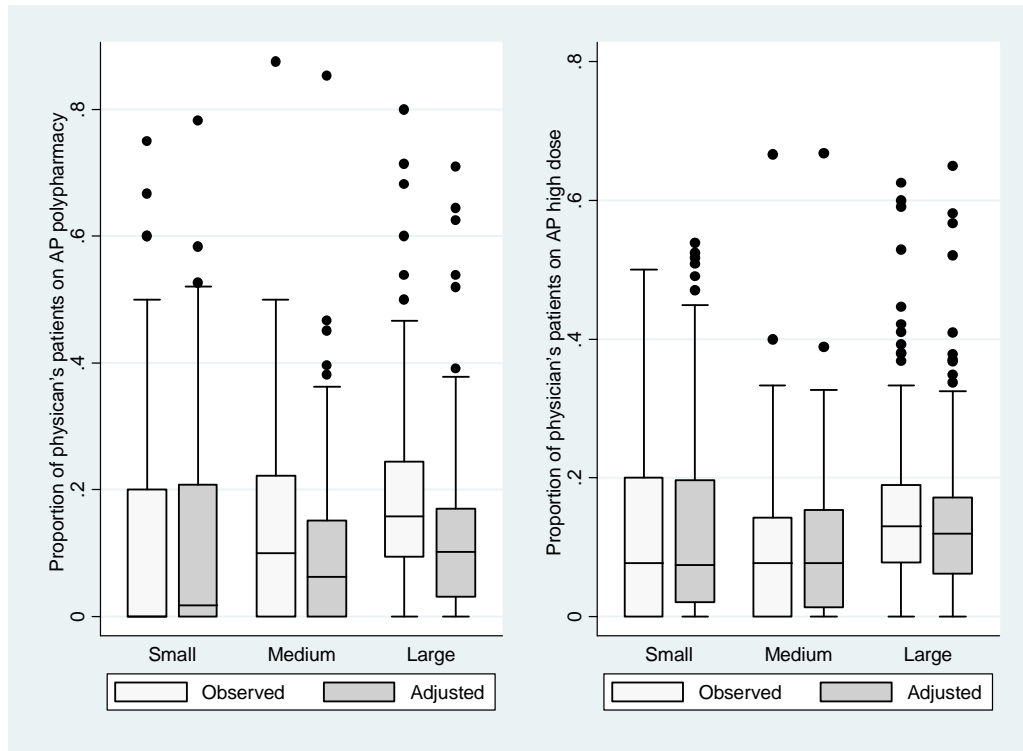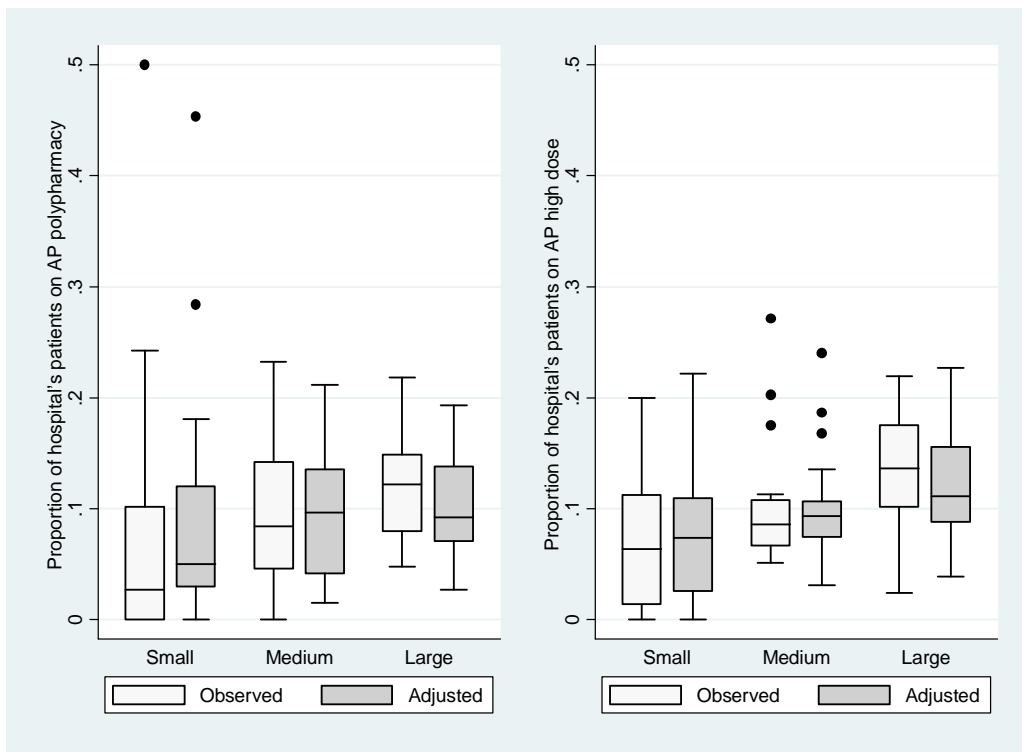
Figure S2. Proportions of physicians' patients on polypharmacy and high doses

Notes:
1. Both graphs show proportions continuously on antipsychotic polypharmacy or high doses over an 11-month period. "Observed" refers to actual, non-adjusted data. See online appendix for method used to adjust for patient characteristics.
2. Small caseload: 163 physicians with 4 to 6 patients (physicians with fewer not included); medium: 134 with 7 – 12; large: 138 with 13 or greater.
3. The upper and lower ends of each box represent the 75th and 25th percentiles of the distribution. The line in between is the median. The whiskers extend to the furthest observation up to 1.5 times the interquartile range. Dots represent outliers that extend beyond that observation.
4. AP= Antipsychotic

Figure S3. Proportions of hospitals' patients on polypharmacy and high doses

Note :
1. Both graphs show proportions continuously on antipsychotic polypharmacy or high doses over an 11-month period. "Observed" refers to actual, non-adjusted data. See online appendix for method used to adjust for patient characteristics.
2. Small number of patients: 20 hospitals with 4 – 54 patients; Medium: 20 with 55 – 146; Large: 20 with 147 and over.
3. See note 3 of Figure 1 for interpretation of box-plots.
4. AP=antipsychotics

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