SUPPLEMENTAL MATERIALS FOR:

Dupouy J, Palmaro A, Fatséas M, et al. Mortality associated with time in and out of buprenorphine treatment in French office-based general practice: a 7-year cohort study. *Ann Fam Med*. 2017;15(4):355-358.

SUPLEMENTARY MATERIAL. DETAILS OF METHODS AND SPECIFIC REFERENCES

We investigated all-cause mortality in a retrospective cohort of subjects newly and exclusively maintained with buprenorphine or buprenorphine/naloxone, from 2006 to 2013, using the "Echantillon Généraliste des Bénéficiaires" (EGB) database. EGB is a permanent representative sample of subjects covered by the French Health Insurance System. The French health insurance system manages, through public entities, all reimbursements of healthcare to all people affiliated to a health insurance scheme in France. EGB is obtained by 1/97th national random sampling with control for distribution of age and gender, and includes approximately 700,000 beneficiaries[1]. The population of the EGB includes insured persons, whether they are receiving healthcare or not.

This database includes demographic, out-hospital reimbursement (including drug dispensing), medical (costly long-term diseases, occupational diseases, sick-leaves...), and in-hospital data[2,3]. All these data are prospectively recorded, individualized, made anonymous and linkable. Limitations concerning out-hospital healthcare data comprise that indications are not recorded neither the results of paraclinical examinations. For drugs, reimbursement data are available but not prescription data (duration of prescription is not known); over-the-counter drugs are not recorded[2]. For in-hospital data, diagnoses codes are available but detailed clinical data are not.

As this is an observational study of anonymized data, based on French regulation, an approval by an ethics committee was not required[4]. Nonetheless, the study protocol was submitted to and approved by the French National Institute of Health and Medical Research (Inserm), which is the Guarantor for access for research purposes to national databases.

Table of details of specific points of method.

Point of method	**Details**
Study population	Subjects newly maintained by buprenorphine (or buprenorphine-naloxone) from the population of the main national health insurance system (CNAM-TS) that covers approximately 80% of the French population. This population is representative of the French population in terms of age, gender and mean expenditure reimbursed by individual. As buprenorphine is exclusively dispensed in community pharmacies, we studied only outpatients.
Inclusion criteria	Subjects had to have their first dispensing of buprenorphine or buprenorphine-naloxone between January 1st, 2007 and December 31, 2011 and not have been exposed to any opiate maintenance treatment OMT (including buprenorphine, buprenorphine-naloxone and methadone) during the previous twelve months. Inclusion criterion was age between 16 and 60 at the time of the first prescription of buprenorphine or buprenorphine-naloxone.
Identification of opiate maintenance treatments	Anatomical Therapeutic Chemical classification system ATC codes[5]: N07BC01 for buprenorphine, N07BC02 for methadone, and N07BC51 for buprenorphine-naloxone.
Exposure to buprenorphine maintenance treatment	Exposure to buprenorphine maintenance treatment (BMT: buprenorphine and buprenorphine-naloxone) was considered as a time-dependent variable. Buprenorphine and buprenorphine/naloxone were considered equally and switches were not studied.

Definition of different buprenorphine exposure periods	To define different buprenorphine exposure periods, we considered that a patient was retained in buprenorphine treatment if he received regular reimbursements, taking into account potential interruption periods. A period of more than 35 days between two reimbursements was considered as treatment interruption. The definition of buprenorphine retention takes into account the specific prescription and dispensing conditions of these medications (prescription for a maximum of 28 days, addition of a seven-day period). This duration of 35 days has been validated in other studies on French Health Insurance System databases[6].
Buprenorphine period duration	Buprenorphine period duration was the duration between the first and the last reimbursement of the period, plus the number of reimbursed Defined Daily Doses (DDD) of the last reimbursement. We used DDD as defined by the World Health Organization[7].
Outcome	All-cause mortality. The date of death is encoded in the EGB from the national death register of the French National Statistics Agency (Institut National de la Statistique et des Etudes Economiques INSEE).
Crude mortality rate	Crude mortality rate was estimated and compared to crude mortality rate of subjects in the EGB aged 16 to 60 during the same period.
Censoring	Data were right-censored at the end of the study period (December 31, 2013) or censoring (death or drop out).

<table>
<tr><td>Charlson’s comorbidity score</td><td>Charlson’s comorbidity score was calculated using codes defined by a specific algorithm, using drug dispensing, and identified diseases (International Statistical Classification of Diseases and Related Health Problems 10th Revision ICD10 codes)[8]. The Charlson score takes into account several comorbidities adjusted to risk of mortality. A score of zero indicates that no comorbidities were found.</td></tr>
<tr><td>Psychiatric diseases were identified</td><td>Health insurance coverage for chronic psychiatric disease, hospital admission for psychiatric disease (case mix classification “Groupe Homogène de Séjour” (GHS) and ICD10 codes)
<table>
<tr><th>Hospital admission</th><th>GHS codes</th><th>PMSI</th></tr>
<tr><td>For a psychiatric disease</td><td>7000, 7001, 7002, 7003, 7004, 7050, 7051, 7052, 7053, 7054, 7055, 7056, 7057, 7058, 7059, 7060, 7061, 7062, 7063, 7064, 7065, 7066, 7067, 7068, 7069, 7070, 7071, 7072, 7073, 7074, 7075, 7076, 7077, 7078, 7079, 7080, 7081, 7082, 7083, 7084, 7085, 7086, 7087, 7088, 7089, 7090, 7091, 7092, 7093, 7094, 7095, 7096, 7097, 7098, 7099, 7100, 7101, 7102, 7103, 7104, 7105, 7106, 7107, 7108, 7109, 7110, 7111, 7113, 7114, 7115, 7116, 7117, 7118, 7119, 7120, 7121, 7122, 7123, 7124, 7125, 7126, 7127, 7128, 7129, 7130, 7131, 7132, 7133, 7134, 7135, 7250, 7251, 7252, 7253, 7254, 7255, 7256, 7257, 7258, 7259, 7260, 7261, 7262, 7263, 7264, 7265, 7266, 7267, 7268, 7269, 7270, 7271, 7272, 7273, 7274, 7275, 7276, 7277, 7278, 7279, 7280, 7281, 7282, 7283, 7284, 7285, 7286, 7287, 7288, 8034, 8291, 8292, 8315, 8316</td><td>principal or associated diagnoses of the ICD10 class F</td></tr>
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Reimbursed psychotropic drugs	Identification by their ATC code throughout the study period: opioid analgesics (N02A), antiepileptics (N03A excluding clonazepam), antipsychotics (N05A), benzodiazepines (N05BA, N05CD, N05CF, and N03AE01 (clonazepam)), antidepressants (N06A), drugs for alcohol dependence (N07BB). If drugs were reimbursed, it means they were prescribed.
Socio economic factors taken into account	Complementary private insurance, universal insurance coverage; status of the beneficiary (insured person or his relative), social deprivation index (FDep 2008 version), an ecological estimator of social deprivation [9]. Universal insurance coverage is coverage for those unemployed and with low income. It is thus an indicator of a poor socio economic level.
Statistics	Qualitative variables were expressed in numbers and percentages and compared between the alive and deceased groups using the chi-square test or Fisher's exact test; quantitative variables as means and standard deviations, and compared using the Wilcoxon rank test. A Cox proportional hazards model was constructed to assess mortality. The alpha risk threshold was set at 0.20 for selecting variables entered in the multivariate model. Time-dependent BMT exposure was tested using the Cox model in univariate (and multivariate) analysis (backward procedure, $\alpha = 5\%$). Data analysis was carried out using SAS Guide43 ® software (SAS Inst., Cary, North Carolina, USA).

References

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