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Hypovitaminosis D is associated with depression and anxiety in schizophrenia: results from the national FACE-SZ cohort. Running title: hypovitaminosis D, depression and anxiety in schizophrenia

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Prescription of Potentially Inappropriate psychotropic drugs in Homeless people with Schizophrenia and Bipolar Disorders. Results from the French Housing First (FHF) program.

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Abstract

Background. Guidelines have been edited for the treatment of schizophrenia (SZ) and bipolar disorders (BD). Background regimen is currently recommended for both illnesses (antipsychotic drug for SZ and mood stabilizer for BD). The recommendations are less clear for major depression in these disorders. Long-term anxiolytic and hypnotic prescriptions may have potential side effects and should be withdrawn as soon as possible.

Objective. The aim of this study was to investigate the prevalence and associated factors of Potentially Inappropriate Psychotropic drugs (PIP) in a large multicenter sample of Homeless Schizophrenia (SZ) and Bipolar Disorder (BD) (HSB) patients.

Methods. This multicenter study was conducted in 4 French cities: Lille, Marseille, Paris and Toulouse. PIP was defined by at least one item among: (i) absence of background regimen (antipsychotic for SZ or mood stabilizer for BD), (ii) absence of antidepressant for major depressive disorder and (iii) daily long-term anxiolytic or (iv) hypnotic prescription.

Results. Overall, 703 HSB patients, mean aged 38 years and 82.9% men were included, 487 SZ (69.3%) and 216 BD (30.7%). 619 (88.4%) of the patients reported at least one PIP. 386 (54.9%) patients had an inappropriate background regimen prescription (209(43.4%) of SZ had no antipsychotic prescription and 177(81.9%) of BD no mood stabilizer), 336 (48%) had an inappropriate antidepressant prescription (with no significant difference between SZ and BD), 326 (46.4%) had an inappropriate prescription of anxiolytics and 107 (15.2%) had an inappropriate prescription of hypnotics. 388(55%) of the subjects were diagnosed with major depression but only 52(13%) of them were administered antidepressants. In multivariate analysis, PIP was associated with bipolar disorder diagnosis (aOR=4.67 [1.84-11.89], p=0.001), current major depressive disorder (aOR=27.72 [9.53-80.69], p<0.0001), lower rate of willingness to ask for help (aOR=0.98[0.96-0.99], p=0.001). Potentially inappropriate background regimen prescription was associated with bipolar disorder diagnosis (aOR=6.35 [3.89-10.36], p<0.0001), lower willingness to ask for help (aOR=0.99[0.98-0.99], p=0.01) and lack of lifetime history of psychiatric care (aOR=0.30[0.12-0.78], p=0.01). Inappropriate antidepressant prescription was associated with antisocial personality disorder (aOR=1.58 [1.01-2.48], p=0.04) and current substance use disorder (aOR=2.18[1.48-3.20], p<0.0001).

Conclusion. The present findings suggest that almost 9 on 10 HSB subjects may receive a PIP including inappropriate prescriptions or absence of appropriate prescription. Bipolar disorder

and/or major depression should be targeted in priority and treated with mood stabilizers and/or antidepressants in this population, while anxiolytics and hypnotics should be withdrawn as much as possible. Major depression should be particularly explored in subjects with comorbid antisocial personality disorder and substance use disorder. The psychiatric care has been associated with better appropriate psychotropic prescriptions and should be reinforced in this population.

Keywords. Schizophrenia; Bipolar Disorders, Homelessness, potentially inappropriate psychotropic drug prescription

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The current clinical trial number is NCT01570712.

Introduction

Schizophrenia (SZ) and Bipolar Disorders (BD) are over-represented in homeless populations compared to non-homeless populations. The prevalence of SZ in homeless people is estimated to be 11% (range 4–16%) (Folsom and Jeste, 2002). Preliminary data for bipolar disorders suggest that their prevalence may be higher, around 15% (Welsh et al., 2012). The management of Homeless Schizophrenia or Bipolar Disorders (HSB) patients is challenging because this sub-population of homeless people is among the most vulnerable and hardest to reach (Auquier et al., 2013). Some guidelines have been published in the treatment of SZ and BD in the general population (Hasan et al., 2015; Howes et al., 2017; Keating et al., 2017; Lehman et al., 2004; Lo et al., 2016; Ravindran et al., 2016; Samalin et al., 2013; Stahl et al., 2013; Taylor and Perera, 2015). In summary, a background regimen is currently recommended for both illnesses (antipsychotic drug for SZ and mood stabilizer for BD). Major Depressive Disorder is a frequent comorbidity of SZ (Andrianarisoa et al., 2017; Fond G., et al., 2018) and bipolar depression remains a major therapeutic challenge (Baldessarini et al., 2018). The use of long-term anxiolytics and hypnotics is not recommended in both illnesses due to physical dependency and potential cognitive and behavioral side effects (Fond et al., 2017a, 2015). The application of these recommendations is rarely made in clinical practice in France (Henry et al., 2011; Schürhoff et al., 2015) and no data is available to date in the HSB population.

The aim of this study was therefore to determine the prevalence of Potentially Inappropriate Psychotropic drugs Prescriptions (PIP) and their associated factors in a large multicenter sample of HSB subjects.

Methodology

Study design and population

The French Housing First program was a multicenter randomized controlled trial conducted in 4 large French cities: Lille, Marseille, Paris and Toulouse (Tinland et al., 2013). The inclusion criteria were as follows: age over 18 years; absolute homelessness (i.e., no fixed place to stay for at least the past 7 nights with little likelihood of finding a place in the upcoming month) or precarious housing situation (housed in single-room occupancy, rooming house, or hotel/motel as a primary residence AND a history of 2 or more episodes of being absolutely homeless in the past year OR one episode of being absolutely homeless for at least 4 weeks in

the past year); diagnosis of SZ or BD by a psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV-TR) criteria (American Psychiatric Association, 2000); and the ability to speak French. Mobile mental health outreach teams recruited patients from August 2011 to April 2014 in the street, emergency shelters, hospitals and jails. Psychiatrists and research assistants performed the evaluations during face-to-face interviews in the offices of the mobile mental health outreach teams, which were located in the downtown area of each city.

Data collection

The following data were collected:

- Sociodemographic information: gender, age, education level.
- Any lifetime contact with a psychiatric care was reported.
- Illness characteristics: Diagnoses (schizophrenia, bipolar disorder, major depressive disorder, Substance use disorder, alcohol use disorder, antisocial personality disorder) were assessed with section L of the MINI (Sheehan et al., 1998). A lifetime history of psychiatric care was reported.
- Drug information: drug class (antipsychotic, mood stabilizers, antidepressant, anxiolytic) and adherence assessed with the French version of the Medication Adherence Rating Scale (MARS) (Fond et al., 2017b; Zemmour et al., 2016) were reported. The MARS is a 10-item, multidimensional, self-reporting instrument that describes a global level of adherence (index). Higher scores indicate a higher likelihood of medication adherence.

PIP definition

Primary outcome was PIP, defined by at least one PIP criterion among: (i) inappropriate background regimen (absence of antipsychotic for SZ or absence of mood stabilizer for BD), (ii) potentially inappropriate antidepressant prescription (defined by the absence of antidepressant for patients with major depression), potentially inappropriate (iii) anxiolytic and (iv) hypnotic prescription (defined by a long-term prescription of anxiolytics and/or hypnotics).

Secondary outcomes were potentially inappropriate background regimen prescription, potentially inappropriate antidepressant prescription, potentially inappropriate anxiolytic prescription and potentially inappropriate hypnotic prescription.

Statistical analysis

All variables are presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. The data were examined for normal distribution with the Shapiro-Wilk test and for homogeneity of variance with the Levene test. Univariate associations between demographic and clinical characteristics of patients with respectively PIP, inappropriate background regimen, inappropriate antidepressant prescription, inappropriate anxiolytic and hypnotic prescriptions were performed using the chi-square test for categorical variables. Continuous variables were analyzed with Student t-tests for normally distributed data and Mann-Whitney tests in case of non-normal distributions. Multivariate analyses using multiple logistic regressions were then performed to determine variables potentially associated with primary and secondary outcomes. PIP, potentially inappropriate background regimen prescription, potentially inappropriate antidepressant prescription, potentially inappropriate anxiolytic and hypnotic prescriptions were considered as separate dependent variables. The variables relevant to the models were selected from the univariate PIP analysis based on a threshold $p\text{-value} \leq 0.20$. Any lifetime history of any contact with a psychiatric care was forced in the models because of its clinical interest.

All of the tests were two-sided. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using the SPSS version 20.0 software package (SPSS Inc., Chicago, IL, USA).

Ethical approval

The study was conducted in accordance with the principles of the Declaration of Helsinki, 6th revision. All participants provided written consent. The local ethics committee (Comité de Protection des Personnes Sud-Méditerranée V, France: trial number 11.050) and the French Drug and Device Regulation Agency (trial number 2011-A00668-33) approved the study.

Results

Overall, 703 HSB patients, mean aged 38 years and 82.9% men were included, 487 SZ (69.3%) and 216 BD (30.7%). 388 (55.4%) were identified with current major depressive disorder, 52 (13.5%) were administered an antidepressant (20(8.1%) for SZ and 32 (23.2%) for BD). 616 (92.3%) had a lifetime history of psychiatric care. 619 (88.4%) of the patients reported

at least one PIP (1 PIP for 236 patients (33.7%), 2 PIP for 252 (36%), 3 PIP for 111 (15.9%) and 4 PIP for 20 (2.9%)). 386 (54.9%) patients were identified with potentially inappropriate background regimen prescription (209(43.4%) of SZ had no antipsychotic and 177(81.9%) of BD had no mood stabilizer prescription), 336 (48%) with potentially inappropriate antidepressant prescription, 326 (46.4%) with potentially inappropriate prescription of anxiolytics and 107 (15.2%) with potentially inappropriate prescription of hypnotics. 388(55%) of the subjects were diagnosed with major depression (138(63.9%) of BD and 246 (51.4%) of SZ) but only 52(13%) of them were administered antidepressants (226 (47.2%) of the SZ patients and 106 (49.1%) of the BD had an inappropriate prescription of antidepressants, $p=0.64$). In multivariate analysis, PIP was associated with bipolar disorder diagnosis (aOR=4.67 [1.84-11.89], $p=0.001$), current major depressive disorder (aOR=27.72 [9.53-80.69], $p<0.0001$), lower rate of patient's willingness to ask for help (aOR=0.98[0.96-0.99], $p=0.001$) (table 1). No significant association with history of homelessness, history of psychiatric care or addictive behavior has been found (all $p>0.05$). Potentially inappropriate background regimen prescription was associated with older age (aOR=1.04 [1.02-1.06], $p<0.0001$), bipolar disorder diagnosis (aOR=6.35 [3.89-10.36], $p<0.0001$), higher current illness severity (aOR=1.26[1.03-1.53], $p=0.02$), lower willingness to ask for help (aOR=0.99[0.98-0.99], $p=0.01$) and lack of lifetime psychiatric care (aOR=0.30[0.12-0.78], $p=0.01$) (table 2). Inappropriate antidepressant prescription was associated with antisocial personality disorder (aOR=1.58 [1.01-2.48], $p=0.04$) and current substance use disorder (aOR=2.18[1.48-3.20], $p<0.0001$) (table 3). Inappropriate anxiolytic and hypnotic prescription were both associated with major depressive disorder (respectively aOR=2.45[1.67-3.58], $p<0.0001$ and aOR=1.73[1.03-2.91], $p=0.04$) (data not shown). No association with adherence into treatment has been found in the five models (all $p>0.05$).

Discussion

The results of the present study may be summarized as follows: in a large multicentric sample of HSB subjects, 88% were identified with at least one PIP, mostly an absence of background regimen, an absence of antidepressants in patients with major depression and a long-term prescription of anxiolytics. PIP was associated with higher diagnoses of bipolar disorder and major depressive disorder, and less importantly with patients' lower willingness to ask for help. The absence of antidepressant prescription in patients with major depression was associated

with comorbid antisocial personality disorder and substance use disorder, while potentially inappropriate anxiolytic and hypnotic prescriptions were associated with major depressive disorder. No association with adherence into treatment has been found. A history of psychiatric care was associated with increased rates of antipsychotics and mood stabilizers prescriptions.

The first finding of the present study is the very high rate (88%) of PIP in a non-selected large multicentric sample of homeless subjects with SZ or BD. No comparable data is available to date, in other homeless populations or in non-homeless populations with SZ or BD. Previous studies carried out in housed SZ subjects have shown high rates of potentially inappropriate antidepressant and anxiolytic prescriptions, but not in a so important manner (Berna et al., 2015; Fond et al., 2017a, 2015; Fond G., et al., 2018). These results should therefore be replicated in other samples to confirm that this high rate is due to the homeless status. It may be reasonably hypothesized that these populations may differ in term of Potentially Inappropriate Psychotropic drug prescriptions (Paudyal et al., 2017). One explanation to this high rate is the “harm reduction” approach to cope with this “hard to reach” population. The patient may accept the anxiolytic but refuse the antipsychotic or the mood-stabilizing drug. The clinician will try to access her/his demand in a first step, to develop further trust, adherence into treatment, psychoeducation and background regimen onset.

The present results suggest that bipolar depression remains a major source of PIP (i.e. long-term anxiolytic and hypnotic prescription without background regimen). This phenomenon has also been extensively described in housed BD populations, mostly due to the delay in diagnosis (Drancourt et al., 2013). Major depression has also been identified as a major source of PIP (long-term anxiolytic and hypnotic prescription without antidepressant treatment) in both BD and SZ subjects. Major depression has been diagnosed in more than 55% of the present sample and only 13% of the depressed subjects received an antidepressant. 51.4% of the homeless SZ subjects were identified with major depression, which is twice much higher than the prevalence of major depression in housed SZ subjects in France (28.5%) (Fond G., et al., 2018). The issue of the identification and treatment of major depression has been recently explored in housed SZ subjects (Fond G., et al., 2018). Antidepressants have been shown to be associated with lower depressive symptoms level, however the rate of resistance to antidepressants remains high (Fond G., et al., 2018), which may explain the underprescription of antidepressants in SZ subjects. In the present sample, homeless subjects with major depression

were four times less treated by antidepressants compared to French housed SZ subjects consulting in the Expert Center network (7% vs. 29%) (Fond G., et al., 2018). One explanation is probably that depression is attributed to homelessness in the mind of the caregivers and therefore remains undertreated.

There is still current debate on the prescription of antidepressants in bipolar depression, antidepressants may potentially increase rapid cycling and may have different effects in bipolar I and bipolar II disorders (Baldessarini et al., 2018). In the present study, bipolar I and II disorders have not been distinguished due to the difficulty to put a lifetime diagnosis in homeless populations with potentially increased memory bias. However, the present findings have shown that BD patients with current major depression were not more treated with mood stabilizers than with antidepressants, which suggests that the absence of effective treatment may not be due to psychiatrist's decision in this specific subpopulation.

In the present study, the under prescription of antidepressants was associated with antisocial personality disorder and substance use disorder. This may suggest that HSB subjects with comorbid antisocial disorder or substance use disorder are less prone to be correctly treated in case of comorbid major depression. This may be explained by the treating psychiatrist being afraid of a manic shift with aggressive behavior in subjects with bipolar/schizoaffective disorder and comorbid antisocial personality disorder. While alcohol use disorder has been extensively associated with major depression (Foulds et al., 2015) and especially in homeless people with mental illness (Yoon et al., 2015), alcohol use disorder has not been associated with any PIP in the present study, which suggests that alcohol use disorder does not impact prescription behavior in HSB subjects. As anxiolytics are used for alcohol withdrawal management in patients with alcohol use disorder, it may have been expected that this comorbidity would be associated with increased long-term anxiolytic prescription, which was not the case in the present results. Anxiolytics and hypnotics long-term prescriptions have been associated with major depression, which suggests that these patients are more prone to be treated by anxiolytics and/or hypnotics than with antidepressants. In the light of these results, increasing the exploration and treatment of major depression in HSB subjects with major depression should be recommended.

A history of at least punctual psychiatric care has been identified in more than 9 on 10 patients (probably due to the free universal access to healthcare system in France) and has been associated with lower inappropriate background regimen in the present study, which suggests

that each homeless subject should receive a psychiatric interview with a special focus on bipolar disorder and major depression detection and treatment to improve the mental health status of this population.

The present study has explored the potentially inappropriate prescriptions of psychotropic drugs in homeless subjects with mental illness, however their underpinnings remain to be explored. Our indicators of potentially inappropriate prescription may not be relevant for all the situations and our findings should be now completed with qualitative analyses. Patients, treating psychiatrists and psychologists, caregivers and social workers should be interviewed to analyze medical needs of homeless patients with mental illness and the potential lacks of the current healthcare system to respond to these needs. One may hypothesize that some factors may be due to the patients such as willingness to ask for help and antisocial personality disorder has been taken into account in the present analyses. Hopelessness may lead to decreased willingness to ask for help in homeless people, and willingness to ask for help has been associated with increased PIP (especially in regard of the absence of background regimen) in the present sample. In France, like in other Western countries, it is not possible to administer a psychotropic drug to a patient except for emergency risk (immediate suicidal risk, agitation or violent behavior), which suggest that the acceptance of the patient and insight into illness may be crucial for appropriate prescriptions. No association of PIP and adherence into treatment has been found, which suggests that the risk of PIP is not higher in subjects with low adherence. However the MARS scale does not distinguish the adherence in each psychotropic drugs. Homeless patients may have different adherence levels depending on the perceived/immediate effect of psychotropic drug. Homeless patients may seek the immediate sedative effects of anxiolytics and hypnotics, and refuse background regimens (including mood stabilizers, antipsychotics and antidepressants), which have no immediate impact on alleviating psychic suffering and may have higher side effects. Clinical interviews should determine if homeless subjects seek escaping from their daily reality through psychotropic drugs for example.

Limitations and perspectives. In addition to the above-mentioned limits, this study was limited by the cross-sectional design. No causal inferences can be formally determined, and our findings should thus be interpreted in terms of associations. Future longitudinal studies are needed to confirm our findings. Because our study occurred in large cities, our findings may not be generalizable to homeless people living in smaller cities, where the life conditions and needs

may differ. However, our study included southern and northern cities, thus taking into consideration socioeconomic, cultural and climatic differences. Due to a high risk of memory bias, the full history of psychotropic drugs prescriptions has not been reported. Future studies should evaluate aggressiveness in HSB subjects and determine if antidepressant onset is associated with increased aggressiveness. Complementary agents (omega 3, vitamin D, zinc) could also be discussed as add-on treatments as they have shown effectiveness in housed SZ and BD populations (Schefft et al., 2017). The prescription habits and knowledge about depression of professionals working in the street should be further explored. Future studies should also determine if PIP might be improved after housing HSB patients.

Strengths. The large sample size, the standardized evaluation, the detailed treatments and the lack of previous data on prescriptions behavior in HSB patients may be mentioned in the strength of the present study.

Conclusion

The present findings suggest that almost 9 prescriptions of psychotropic drugs on 10 in HSB subjects may be potentially inappropriate including inappropriate prescriptions or absence of appropriate prescription. Bipolar disorder and/or major depression should be targeted in priority and treated with mood stabilizers and/or antidepressants in this population, while anxiolytics and hypnotics should be withdrawn as much as possible. The rate of untreated depression remains high in both SZ and BD subjects, and SZ were administered more often antipsychotics than BD mood stabilizers. Major depression should be particularly explored in subjects with comorbid antisocial personality disorder and substance use disorder who are less prone to receive antidepressant prescriptions. The psychiatric care has been associated with better rates of appropriate treatment regimens prescriptions and should be reinforced in this population.

Conflicts of interest: no conflicts to disclose.

Authors' contributions

Conception and design: A.T., V.G., Collaborators French Housing First Study Group and P.A.

Study coordination: A.T., V.G., Collaborators French Housing First Study Group and P.A.

Inclusion and clinical data collection: A.T., V.G., and Collaborators French Housing First Study Group

Analysis of data: A.T., M.B., G.F., and L.B.

Interpretation of data: A.T., G.F., and L.B.
Drafting and writing of the manuscript: all of the authors.

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