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Improving the treatment and remission of major depression in homeless people with severe mental illness: the multicentric French Housing First (FHF) program.

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French Housing First Study Group

Running title: Major depression in homeless people with severe mental disorders

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Abstract (limited 250 words)

Aims. The objectives of the present study were to determine the rates and associated factors of (i) MDD, (ii) antidepressant prescription and (iii) MDD non-remission in homeless subjects with bipolar disorder (BD) or schizophrenia (SZ).

Methods. This multicenter study was conducted in 4 French cities. MDD was defined with the section L of the MINI. Unremitted MDD was defined by current antidepressant treatment and current MDD.

Results. 700 subjects, mean aged 38 years and 82.5% men were included: 55.4% were diagnosed with MDD but only 10.4% were administered antidepressants. Violent victimization in the past 6 months, alcohol use disorder and current substance abuse disorder were associated with increased rates of MDD. 71.2% antidepressant-treated subjects were unremitted. BD diagnosis and substance abuse disorder were found to be associated with increased risk of unremitted MDD. BD-MDD patients were found to be twice more frequently administered antidepressants than SZ-MDD ones, however the non-remission rates were higher in BD subjects compared to SZ. No antidepressant class and no specific antipsychotic or mood stabilizer has been associated with higher or lower rates of remitted MDD.

Conclusion. MDD seems to be highly prevalent, underdiagnosed and undertreated in BD and SZ homeless subjects. Beyond antidepressants, add-on strategies including complementary agents, lithium, lamotrigine/carbamazepine or anti-inflammatory drugs and the specific care of alcohol and substance use disorders may be recommended to improve the prognosis of this specific population in addition to other interventions including housing and resocialization. Violent victimization is also frequent and should be specifically prevented in this vulnerable population.

Keywords. Schizophrenia; Bipolar Disorders, Homelessness; major depression; antidepressant.

Introduction

Treating Major Depressive Disorder (MDD) remains a therapeutic challenge in both schizophrenia (SZ) and bipolar disorders (BD). In schizophrenia, MDD is underdiagnosed, undertreated, with lower rates of remission under antidepressant treatments compared to non-SZ MDD subjects (Andrianarisoa et al., 2017; Guillaume Fond et al., 2018a). Bipolar depression remains a major challenge and a debate is ongoing to determine if antidepressant prescription should be recommended in bipolar depressed patients. A recent meta-analysis has concluded that reduced new depressive episodes may be achieved by long-term antidepressant treatment with no significantly increased risk of new manic/hypomanic episodes in BD (Liu et al., 2017). **While SZ and BD remain highly prevalent in homeless people (Ayano et al., 2019; Welsh et al., 2012)**, little is known about MDD in this specific population, its prevalence and the effectiveness of psychotropic drugs. Additional factors including alcohol and substance use disorders that are highly prevalent in homeless subjects may also play a major role in depression diagnosis and remission under treatment (Lim et al., 2016).

The objectives of the present study were to determine the MDD prevalence and associated factors in homeless subjects with BD and SZ, the rates of patients treated by antidepressants, the factors associated with antidepressant prescription, the rate of unremitted MDD patients under antidepressants and the factors associated with non-remission.

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. The current analysis included only baseline data (t0, before any intervention).

MDD, treated MDD and unremitted MDD definitions

MDD was defined with the section L of the MINI (Sheehan et al., 1998). Treated MDD was defined by the administration of at least one antidepressant for more than 8 weeks at the time of evaluation. There is no consensual definition to date of remitted MDD in subjects with severe mental disorders to date. As the present study was an ecological/observational study, non-remitted MDD was proxy by current antidepressant treatment for at least 8 weeks at the time of the evaluation (Guillaume Fond et al., 2018b).

Data collection

The following data were collected:

- Sociodemographic information: gender, age.
- Illness characteristics: Diagnoses (SZ, BD, alcohol use disorder, substance use disorder) were assessed with section L of the MINI (Sheehan et al., 1998).
- Drug information: drug classes (antipsychotic, mood stabilizers, antidepressant) were reported. A specific group including olanzapine, quetiapine and aripiprazole (the three antipsychotics approved for the treatment of bipolar depression) has been analyzed to determine if these prescriptions were associated with lower depression rates and higher remission rates under antidepressants in BD subjects.

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 was examined for normal distribution with the Shapiro-Wilk test and for homogeneity of variance with the Levene test. Comparisons of demographic, clinical and treatment characteristics between MDD

and non-MDD patients (**Table 1**), treated and untreated (**Table 2**) and remitted MDD and unremitted MDD (**Table 3**) were performed using the chi-square test for categorical variables and Student t-tests or Mann-Whitney for continuous variables.

Three multivariate logistic regressions were performed to determine which demographic, clinical and treatment characteristics were associated with MDD, antidepressant prescription and non-remission. The variables relevant to the models were selected from the univariate analysis, based on a threshold P-value ≤ 0.20 . Two additional variables were included in the models because of its sociodemographic interest (age and gender). The final models incorporated the adjusted Odds Ratios (aOR) and their corresponding 95% confidence interval (CI).

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, 700 HSB patients, mean aged 38 years and 82.5% men were included (479 (68.9%) SZ and 216(31.1%) BD, 5 missing diagnoses). Current MDD was diagnosed in 388 (55.4%) of the subjects (138/216 (63.8%) for BD vs. 246/479 (51.3%) for SZ) while only 73 (10.4%) patients were treated by antidepressants. 420 (62.5%) reported a history of violent victimization in the past 6 months. BD patients with MDD were found to be twice more frequently administered antidepressants than SZ patients with MDD (39/145 (26.8%) for BD vs. 34/260 (13.1%) for SZ).

Compared to patients without MDD, MDD patients were found to have been more frequently victim of violence in the past 6 months (aOR=1.58[1.13-2.20], $p=0.01$), current

alcohol use disorder (aOR=1.41[1.01-1.97], $p=0.04$), current substance abuse disorder (aOR=2.27[1.63-3.18], $p<0.0001$) (**Table 1**, univariate and multivariate analyses).

Compared to untreated MDD patients, patients being administered antidepressants were found to be slightly older (41.4 years vs. 38.7 years, aOR =1.03[1.01-1.06], $p=0.04$), to be more frequently bipolar (aOR=2.42[1.33-4.41], $p=0.003$), to have been more frequently victim of violence in the past 6 months (aOR=2.33[1.24-4.35], $p=0.01$) to have more frequently substance use disorders (aOR=1.83[1.02-3.30], $p=0.04$) (**Table 2**, univariate and multivariate analyses). Antidepressant treatment was not associated with increased current manic shift (38(13.4%) for patients without antidepressants vs. 13(18.8%) for those taking antidepressants, $p=0.24$), but were associated with a history of manic shift (36(13.1%) for patients without antidepressants vs. 18(27.7%) for patients with antidepressants, $p=0.004$) (data not shown).

Overall, 52 (71.2%) antidepressant-treated subjects were still diagnosed with MDD (=“unremitted MDD”) (32/39 (82.0%) for BD vs. 20/34 (58.8%) for SZ). BD subjects (aOR=3.13[1.01-9.76], $p=0.04$) and patients with substance abuse disorder (aOR=3.92[1.23-12.47], $p=0.02$) were found to be at increased risk of unremitted MDD compared to remitted patients (**Table 3**, univariate and multivariate analyses).

No antidepressant class (SSRI, NSRI) and no antipsychotic has been associated with higher or lower rates of remitted MDD (all $p>0.05$, data not shown). None of the participants treated by antidepressants was treated with clozapine, lithium, lamotrigine or carbamazepine, dietary complementary agents or anti-inflammatory drugs.

Discussion

The results of the present study may be summarized as follows: in a large multicentric sample of HSB subjects mean aged 38 years and 82% men, more than half was diagnosed with current major depressive disorder, while only 10% were treated by antidepressants and more than 70% of those treated remained with major depression at the time of the evaluation. History of violent victimization, alcohol and substance use disorder were found to be associated with increased MDD. Bipolar patients and those with history of violent victimization and substance use disorder were more frequently prescribed antidepressants, and among them bipolar patients and those with substance use disorder were more frequently unremitted under treatment.

Major depression has been found to be highly prevalent both in BD (64%) and SZ (51%) subjects, while BD subjects were twice more frequently prescribed antidepressants (27% vs. 13%). This result was not expected, as antidepressant prescription benefit/risk ratio has been extensively debated in bipolar depression (Baldessarini et al., 2018). Treatments have limited effectiveness and a debate is ongoing to determine if BD patients with MDD should be treated by antidepressants or not, some authors arguing that antidepressants may do more harm than good by increasing rapid cycling and manic shifts. Antidepressants have been found to be associated with past history of manic shift but not with current mania in our sample, which is in favor of a recommendation of careful prescription of antidepressants in patients at risk of manic shift (and especially aggressive manic shift). This risk may explain the very low rate of antidepressant prescription in our sample.

Bipolar depression remains a major challenge for both housed and unhoused BD patients. Mood stabilizers and antipsychotics (olanzapine, aripiprazole, low-doses quetiapine) are currently recommended as treatments of reference in bipolar depression. However, neither valproate, olanzapine, aripiprazole or quetiapine have been associated with higher rates of remitted MDD in the present sample, and lithium, carbamazepine, lamotrigine and clozapine were not administered in the present sample of patients with unremitted MDD. It is therefore not possible to conclude from the present results that mood stabilizers are not effective in major depression in SZ and BD homeless subjects. However, there is a clear underprescription of these drugs in this population that may result from doctor and patient factors. From the doctor's point of view, lithium may be associated with lethal risk in case of overdose, carbamazepine is associated with the pharmacokinetic drug interactions and lamotrigine may be associated with acute immune-allergic cutaneous rash with potential lethal risk. All these prescription limits may induce a prescription bias. From the patient point of view, adherence into treatment may be better for drugs with an immediate effect (*i.e.*, the drugs helping escaping reality rather than coping with it, including anxiolytic and hypnotic drugs (G. Fond et al., 2018c)).

One may have expected that SZ subjects would be more likely to be administered antidepressants, given that antidepressants have shown effectiveness in SZ patients (Guillaume Fond et al., 2018b) and that the risk of manic shift is lower in schizophrenia compared to bipolar disorders. On the contrary, SZ patients were administered lower rates of antidepressants despite more than a half being diagnosed with major depression. This phenomenon is not limited to

homeless subjects and has been previously found in housed stabilized SZ subjects (Guillaume Fond et al., 2018b). Depression may be confounded with negative symptoms of schizophrenia (including blunted affect, anhedonia and lack of motivation). Treating psychiatrists may also be afraid of psychotic activation under antidepressants or drug interactions (through cytochrome modulation), however there is no supportive evidence for a psychotic activation under antidepressants and most of second-generation antidepressants have no interaction with antipsychotic drugs. The present results suggest that clinicians treating homeless subjects should always explore major depression in SZ subjects, by targeting specific mood symptoms including sadness, early awakening and suicidal ideation for example.

It should be underlined that the remission rates are much lower than in non-homeless BD and SZ populations. In the present sample, 59% of the SZ subjects were still diagnosed with MDD despite an antidepressant treatment, vs. 44% of the housed SZ subjects of a previous French study (Guillaume Fond et al., 2018b). Several factors may explain this discrepancy, including age (the present sample was 6 years older on average than the previous study) and comorbidities (substance use disorder being more frequent in homeless subjects and having been associated with non-remission in the present sample). Another explanation may be due to higher rates of nutritional deficiencies in homeless subjects. No patient was found to be administered complementary agents, while omegas 3, vitamin D and methylfolate have shown effectiveness in the treatment of MDD in the general population in recent high-quality meta-analyses (Sarris et al., 2016; Schefft et al., 2017). Given that homeless subjects are at high risk of poor-quality food intake, this strategy should be specifically tested due to its high benefit/risk ratio. While homeless subjects may be at increased risk of chronic inflammation and while chronic peripheral inflammation has been associated with resistance to treatment in severe mental disorders (G. Fond et al., 2018b), none of the patients was administered anti-inflammatory drugs. These drugs should be also evaluated as a potentially useful treatment strategy in homeless subjects with severe mental disorders. Vitamin D supplementation has also shown effectiveness in housed patients with severe mental disorders and should be evaluated in homeless ones (G. Fond et al., 2018a).

These strategies should be combined with social interventions including housing programs for housing stability and family interventions for substance use outcomes (Wang et al., 2019). Community engagement to build a collaborative approach to implementing depression

quality improvement across diverse programs has shown to be more effective than resources for services for individual programs in improving mental HRQL, physical activity and homelessness risk factors (Wells et al., 2013). Promoting mobile phone technologies could also improve other outcomes in this population (Raven et al., 2018).

Patients with alcohol use disorder and substance use disorder were found to have higher rates of MDD and antidepressant prescription. These results suggest that addiction is not a motive for underprescription of antidepressants in our sample, while the debate to prescribe antidepressants in subjects with alcohol use disorder before or after alcohol withdrawal is still open (Foulds et al., 2015). Our results suggest that alcohol use disorder was not associated with increased non remission rates, it seems therefore reasonable to recommend the prescription of antidepressants in homeless subjects with BD/SZ and alcohol use disorder. This preliminary result should be confirmed by clinical trials. Further studies should also determine the reasons why substance use disorder has been associated with increased rates of non-remission under antidepressants in our sample. Several hypotheses may be suggested. First, these patients may have more adherence issues that have been extensively described elsewhere (Paudyal et al., 2017; Zemmour et al., 2016). Second, antidepressants may have lower intrinsic efficacy in this population due to differences in neuronal pathways activation, according to the substance intake. Managed alcohol programs and other alcohol-targeted interventions should be developed in homeless subjects with severe mental disorders (Pauly et al., 2019) as well as Mindfulness-Oriented Recovery Enhancement that has shown effectiveness in Co-Occurring Substance Dependence, Traumatic Stress, and Psychiatric Disorders (Garland et al., 2016).

Subjects reporting history of violent victimization were found to be at increased risk of MDD in the present study. This result is consistent with previous findings (Mackelprang et al., 2014; Satyanarayana et al., 2015; Tong et al., 2019; Wong et al., 2016) and suggest that violent victimization should be prevented in this vulnerable population. Individuals with lived experience of homelessness face considerable marginalization, dehumanization and structural violence. It has been shown that re-entering housing may decrease the risk of victimization (Tong et al., 2019). While some intimate partner violence survivors require extensive and possibly long-term assistance to achieve safe and stable housing (especially if they are contending with multiple complex issues), others could avoid homelessness if provided with immediate, individualized, and flexible assistance (Sullivan et al., 2019). Practitioners and social

service providers should also consider anti-oppressive approaches and provide, refer to, or advocate for health and structural interventions using the principles of trauma-informed care(Magwood et al., 2019).

Limits and perspectives. Some limits of the French Housing First trial have been previously described(G. Fond et al., 2018c). 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. Persecutory delusion has been recently identified as a risk factor for non-remission in depressed SZ housed subjects (Guillaume Fond et al., 2018b) and has not been reported in the present study, as well as education level. Psychotic symptomatology should be more precisely investigated in future studies assessing major depression in homeless subjects. Daily tobacco smoking has been associated with MDD in the general population and has not been reported in the present study (Rey et al., 2017). History of rapid cycling has not been explored in BD patients due to memory bias issues. The absence of history of treatment data made us unable to define and explore resistance into treatment. Future studies should also include lifestyle evaluations (including diet, physical activity and sleep). The absence of biological data is another limit. Metabolic and inflammatory data and nutritional status may have been useful to explain the rates of MDD and recommend strategies (such as anti-inflammatory strategies or nutritional strategies for example). Yet obtaining biological data is more difficult in homeless patients than in non-homeless due to organizational and individual factors. The limit for lithium prescription may be due to dehydration risk in homeless subjects that has not been explored. The sample size for the last analysis was low, which may have limited the statistical power.

Strengths. The strengths of the French Housing First trial have been previously described(G. Fond et al., 2018c), including the large sample size, the standardized evaluation, the detailed treatments and the lack of previous data on prescriptions behavior in homeless patients with severe mental disorders.

Conclusion

More than half of homeless subjects with severe mental disorders are diagnosed with major depression while only 10% being treated by antidepressants. In the light of the present

results, the following strategies (not exhaustively) should be further tested to improve MDD treatment in homeless subjects with severe mental disorders: complementary agents administration (including omega 3, vitamin D, methylfolate), lithium, carbamazepine and lamotrigine onset, anti-inflammatory drugs add-on therapy as indicated combined with the specific care of alcohol and psychoactive substance use disorders in addition to social interventions including housing programs, community engagement, early flexible funding, mobile phone and family interventions. Violent victimization is also frequent and should be specifically prevented in this vulnerable 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.

Data sharing.

Due to ethical concerns, European laws and French Réglementation Générale de la Protection des données (RGPD) the individual data is not available.

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