BJPsych | The British Journal of Psychiatry (2018)
213, 464–470. doi: 10.1192/bjp.2018.87

Remission of depression in patients with schizophrenia and comorbid major depressive disorder: results from the FACE-SZ cohort*

Guillaume Fond, Laurent Boyer, Fabrice Berna, Ophélia Godin, Ewa Bulzacka, Méja Andrianarisoa, Lore Brunel, Bruno Aouizerate, Delphine Capdevielle, Isabelle Chereau, Nathalie Coulon, Thierry D'Amato, Caroline Dubertret, Julien Dubreucq, Catherine Faget, Sylvain Leignier, Christophe Lançon, Jasmina Mallet, David Misdrahi, Christine Passerieux, Romain Rey, Aurélie Schandrin, Mathieu Urbach, Pierre Vidailhet, Marion Leboyer, Franck Schürhoff, Pierre-Michel Llorca and the FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group

Background

Major depressive disorder (MDD) is underdiagnosed and undertreated in schizophrenia, and has been strongly associated with impaired quality of life.

Aims

To determine the prevalence and associated factors of MDD and unremitted MDD in schizophrenia, to compare treated and non-treated MDD.

Method

Participants were included in the FondaMental Expert Centers for Schizophrenia and received a thorough clinical assessment. MDD was defined by a Calgary score ≥6. Non-remitted MDD was defined by current antidepressant treatment (unchanged for >8 weeks) and current Calgary score ≥6.

Results

613 patients were included and 175 (28.5%) were identified with current MDD. MDD has been significantly associated with respectively paranoid delusion (odds ratio 1.8; P = 0.01), avolition (odds ratio 1.8; P = 0.02), blunted affect (odds ratio 1.7; P = 0.04) and benzodiazepine consumption (odds ratio 1.8; P = 0.02). Antidepressants were associated with lower depressive symptoms score (5.4 *v.* 9.5; P < 0.0001); however, 44.1% of treated patients remained in non-remittance MDD. Nonremitters were found to have more paranoid delusion (odds ratio 2.3; P = 0.009) and more current alcohol misuse disorder (odds ratio 4.8; P = 0.04). No antidepressant class or specific antipsychotic were associated with higher or lower response to antidepressant treatment. MDD was associated with Metabolic syndrome (31.4 *v.* 20.2%; P = 0.006) but not with increased C-reactive protein.

Conclusions

Antidepressant administration is associated with lower depressive symptom level in patients with schizophrenia and MDD. Paranoid delusions and alcohol misuse disorder should be specifically explored and treated in cases of non-remission under treatment. MetS may play a role in MDD onset and/or maintenance in patients with schizophrenia.

Declaration of interest

None.

Assessment of major depressive disorder (MDD) in schizophrenia is clinically important because of the high prevalence of depression and suicidality in schizophrenia and its effect on functioning and quality of life.[1] The relationship between psychotic and affective symptoms has been central to the dilemma of psychiatric classification.[2] It has been suggested that some positive symptoms, especially delusions, may be specifically associated with MDD via cognitive biases.[3] Schizophrenia is also associated with increased somatic comorbidities, including metabolic syndrome (MetS), a general metabolic disturbance that has been identified as twice as high in patients with schizophrenia compared to the general population,[4] and chronic low-grade peripheral inflammation that has been associated with cognitive impairment in schizophrenia.[5] Antipsychotics themselves produce extrapyramidal side-effects (particularly bradykinesia, blunted affect and verbal delays which may be confused with the psychomotor retardation of depression.[6] People with schizophrenia are also prone to addictive behaviour, some of which may also produce depressive symptoms.[7] There are no current guidelines for the treatment of MDD in patients with schizophrenia. For example, the National Institute for Health and Care Excellence guidelines make no specific recommendation for the treatment of MDD cooccurring in SZ.[8] Two recent meta-analyses have concluded that antidepressants may be effective in the treatment of MDD in schizophrenia; however, evidence was mixed and conclusions must be qualified by the small number of low- to moderate-quality studies.[9,10] However, there is a robust and current debate on the effectiveness of add-on antidepressant therapy in patients with schizophrenia and MDD. Schizophrenia is also associated with increased somatic comorbidities, including MetS, a general metabolic disturbance that has been identified as twice as high in patients with schizophrenia compared to the general population,[4] and chronic low-grade peripheral inflammation that has been associated with cognitive impairment in schizophrenia.[5] Depression has been associated with metabolic disturbances in schizophrenia including MetS parameters,[11] and chronic peripheral inflammation has been associated with MDD and antidepressant consumption in patients with schizophrenia.[12,13]

The objectives of the present study were to determine the prevalence and associated factors of MDD in schizophrenia, to determine if patients with schizophrenia treated with antidepressants had lower depressive symptoms levels compared with those without antidepressants and to determine the prevalence and associated factors with remission in patients with schizophrenia who were administered antidepressants.

* A full list of collaborators, including all affiliations, is available as supplementary material at https://doi.org/10.1192/bjp.2018.87

https://doi.org/10.1192/bjp.2018.87 Published online by Cambridge University Press

Method

Study design

The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) cohort is based on a French national network of ten Schizophrenia Expert Centres (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg and Versailles), set up by a scientific cooperation foundation in France, the FondaMental Foundation (www.fondation-fondamental.org), and pioneered by the French Ministry of Research to create a platform that links thorough and systematic assessment to research.[14]

Study population

Consecutive, clinically stable patients (defined by no admission to hospital and no treatment changes during the 8 weeks before evaluation) with a DSM-IV,[15] Text Revision diagnosis of schizophrenia or schizoaffective disorder were consecutively included in the study. Diagnosis was confirmed by two trained psychiatrists of the Schizophrenia Expert Centers network. All patients were referred by their general practitioner or psychiatrist, who subsequently received a detailed evaluation report with suggestions for personalised interventions.

Data collected

Patients were interviewed by members of the specialised multidisciplinary team of the Expert Center. Diagnoses interviews were carried out by two independent psychiatrists according to the Structured Clinical Interview for Mental Disorders (SCID v1.0).

Depression and remission under antidepressant definitions

Current depressive symptoms were evaluated by the Calgary Depression Rating Scale for Schizophrenia (CDRS[16,17]). A score of ≥6 is considered as a current major depressive episode. The CDRS is the most widely used scale for assessing depression in schizophrenia. It has excellent psychometric properties, internal consistency, interrater reliability, sensitivity, specificity and discriminant and convergent validity.[16]

There is no consensual definition to date of remitted MDD in patients with schizophrenia to date. As the present study was an ecological/observational study and that all patients were on stable medication for more than 8 weeks, non-remitted MDD was defined as current antidepressant treatment and a CDRS score ≥6 (current MDD episode) at the time of the evaluation.

Sociodemographic, clinical and treatment variables

Information about education level and illness duration was recorded. As the Positive And Negative Syndrome Scale (PANSS) is not suited to differentiate the different delusions and hallucinations,[18] delusions hallucinations and negative symptoms were evaluated by the SCID v1.0[19] as well as current cannabis and alcohol misuse disorder (the presence of at least two symptoms among the 11 explored in DSM-IV indicates an alcohol misuse disorder). PANSS total score was only used for the description of the sample characteristics. Insight was measured by the Birchwood Insight Scale score, a brief self-reported measure.[20,21] Current daily tobacco smoking was self-reported. Ongoing psychotropic treatment was recorded as well as other medication. The antipsychotic treatments were classified according to their Anatomical-Therapeutic-Clinical (ATC) class. First-generation antipsychotics (FGA) were defined by ATC classes N05AA–AC (phenothiazines), NO5AD (butyrophenones) and NO5AF (thioxanthenes). Second-generation antipsychotics were defined by ATC classes N05AH (diazepines, oxazepines, thiazepines and oxepines) and NO5AL (benzamides). Chlorpromazine equivalent dosages were calculated according to the minimum effective dose method.[22] All patients were on stable medication for more than 8 weeks and treated by antipsychotics.

Measurements

A blood draw for routine blood exam was performed and triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total cholesterol as well as glucose (if patients confirmed fasting for at least 10 h) were collected. High-sensitivity C-reactive protein (CRP) was measured with an assay using nephelometry (Dade Behring), blinded to schizophrenia status.

MetS definition

Sitting blood pressure and anthropometrical measurements were recorded in the Expert Centers. Two blood pressure measurements were made 30 s apart in the right arm after the participant had sat and rested for at least 5 min. A third measurement was made only when the first two readings differed by more than 10 mm Hg. The average of the two closest readings was used in the analysis. Waist circumference was measured midway between the lowest rib and the iliac crest with the patients standing. This was performed with a tape equipped with a spring-loaded mechanism to standardise tape tension during measurement. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Overnight fasting blood was collected for metabolic profiles analysis. Fasting levels of serum triglyceride and fasting plasma glucose were measured by an automated system, and serum HDL cholesterol level was measured by electrophoresis. The diagnosis of MetS was defined according to the modified criteria of the International Diabetes Federation,[23] which requires the presence of three or more of the following five criteria: high waist circumference (>94 cm for men and >80 cm for women), hypertriglyceridemia (≥1.7 mM or on lipid-lowering medication), low HDL cholesterol level (<1.03 mM in men and <1.29 mM in women), high blood pressure (≥130/85 mmHg or on antihypertensive medication) and high fasting glucose concentration (≥5.6 mM or on glucose-lowering medication).

Ethical concerns

The study was carried out in accordance with ethical principles for medical research involving humans (World Medical Association, Declaration of Helsinki). The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, 18 January 2010). All data were collected anonymously. As this study includes data coming from regular care assessments, a non-opposition form was signed by all participants. An informed consent has been given by each patient. There was no ethical number according to the French law in 2012 (non-interventional study).

Statistical analysis

Sociodemographics, clinical characteristics, addictive behaviour and treatments are presented as measures of means and dispersion (s.d.) 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. Comparisons between MDD and non-MDD, treated and non-treated MDD and remitted and non-remitted individuals regarding demographic and clinical characteristics were performed with the χ^2 test for categorical variables. Continuous variables were

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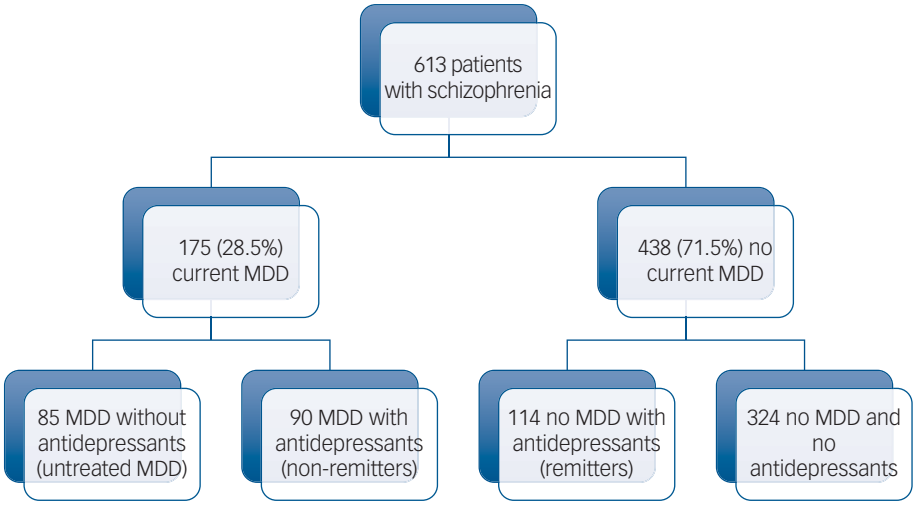

Fig. 1 Study flowchart.

MDD, major depressive disorder.

analysed with Student *t*-tests for normally distributed data and in case of normality violation, additional Mann–Whitney tests were performed to confirm the result.

Variables with *P* values <0.20 in univariate analysis were included in the multivariate logistic regression model of factors associated with MDD and resistant MDD. The final models included odds ratios and 95% confidence intervals. This study was a confirmatory analysis. No correction for multiple testing has therefore been carried out, which is consistent with recommendations.[24] Analyses were conducted with SPSS 17.0 software (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed, with an α level set at 0.05.

Results

Overall, 613 stabilised community-dwelling patients with schizophrenia (mean age 32.3 ± 9.6 years; 73.9% men; mean illness duration 10.7 ± 8.1 years, mean PANSS score 67.4 ± 18.6, mean Birchwood score 8.7 ± 2.8) were included, and 175 (28.5%) were identified with current MDD (see Fig. 1 and Table 1). In multivariate analyses, MDD has been significantly associated with respectively paranoid delusion (odds ratio 1.8; $P = 0.01$), avolition (odds ratio 1.8; $P = 0.02$), blunted affect (odds ratio 1.7; $P = 0.04$) and benzodiazepine consumption (odds ratio 1.8; $P = 0.02$) independently of age, current alcohol misuse disorder, FGA administration and extrapyramidal symptom level (Table 1). Compared with remitted patients, non-remitted patients were found to have more paranoid delusion (odds ratio 2.3; $P = 0.009$) and more current alcohol misuse disorder (odds ratio 4.8; $P = 0.04$) independently of age, avolition, FGA administration and benzodiazepine consumption (Table 2). The antidepressant classes were distributed as follows: selective serotonin reuptake inhibitors ($n = 127$; 20.7%), norepinephrine and serotonin reuptake inhibitors ($n = 53$; 8.7%), tricyclics ($n = 10$; 1.6%), monoamine oxidase inhibitors ($n = 1$; 0.2%) and other antidepressants (including mianserine, mirtazapine, agomelatine and tianeptine) ($n = 24$; 3.9%). No antidepressant class and no specific antipsychotic were associated with higher or lower depressive symptoms level (all $P > 0.05$, data not shown). Including insight in the analyses did not change the response to antidepressant treatment.

MDD was associated with MetS (31.4 *v.* 20.2%; $P = 0.006$) but not with increased CRP ($P > 0.05$). No association between non-remission under antidepressant and biological variables was found in the cohort.

Discussion

Our major findings may be summarised as follows: in a large sample of 613 non-selected community-dwelling out-patients with schizophrenia, MDD has been significantly associated with paranoid delusion, avolition, blunted affect and benzodiazepine consumption after adjustment for sociodemographic factors, other treatments and addictive behaviour. Antidepressants were found to be associated with lower depressive symptoms level; however, almost half of the patients were still classified with current MDD despite unmodified antidepressant treatment for at least 8 weeks. Compared with remitted patients, non-remitted patients were found to have significantly higher paranoid delusion and alcohol misuse disorder after adjustment for sociodemographic variables, treatments and addictive behaviour. MDD was associated with MetS but not with peripheral inflammation.

A total of 28% of our sample was identified with current MDD. This is consistent with most of the previous studies reporting MDD rates of around one-third of patients with stabilised schizophrenia (for review, see Buckley *et al.*[2]). Overall, 44% of patients with MDD treated by antidepressants did not sufficiently respond to antidepressants and remained depressed.

MDD has been associated with avolition and blunted affect. Our study demonstrates the limitations of depression scales (CDRS and PANSS depressive factor) to discriminate depressive symptoms from primary and secondary depressive symptoms in patients with schizophrenia. It may be hypothesised that this limitation may explain the high rate of non-remission under antidepressant in our sample. However, we found no association of unremitted MDD and negative symptoms. The CDRS was initially developed to determine depressive symptoms from schizophrenia-specific symptoms, but our results clearly suggest that this aim was not fully reached, given the strong association of CDRS scores with negative symptoms, especially blunted affect and PANSS negative and depressive subscores. Further studies should determine the

https://doi.org/10.1192/bjp.2018.87 Published online by Cambridge University Press

Table 1 Associations between major depression at baseline (defined by a Calgary score ≥ 6) and sociodemographic characteristics.

	Whole sample (*N* = 613)		No MDD (*n* = 438, 71.5%)		MDD (*n* = 175, 28.5%)		Univariate *P* value	Odds Ratio	95% CI		Adjusted *P* value*
	N or mean	(% or s.d.)	*N* or mean	(% or s.d.)	*N* or mean	(% or s.d.)					
Sociodemographic and illness variables											
Age (years)	32.3	9.6	32.1	9.0	32.8	11.1	0.87	1.0	0.9	1.0	0.78
Gender (male)	453	73.9%	324	74.0%	129	73.7%	0.94	–	–	–	–
Education level (years)	12.2	2.6	12.1	2.6	12.2	2.6	0.59	–	–	–	–
Illness duration (years)	10.7	8.1	10.3	7.6	11.6	9.1	0.28	–	–	–	–
Addictions											
Current cannabis misuse disorder	36	5.9%	25	5.7%	11	6.3%	0.51	–	–	–	–
Current alcohol misuse disorder	36	5.9%	21	4.8%	15	8.6%	0.07	2.9	0.7	2.9	0.12
Current daily tobacco smoking	324	55.3%	232	55.8%	92	54.1%	0.72	–	–	–	–
Clinical symptoms[a]											
Paranoid delusion	**212**	**48.5%**	**134**	**42.5%**	**78**	**63.9%**	**<0.0001**	**1.8**	**1.1**	**1.8**	**0.01**
Mystic delusion	70	12.6%	50	12.6%	20	12.7%	0.98	–	–	–	–
Auditory hallucinations	136	26.1%	94	24.9%	42	29.2%	0.31	–	–	–	–
Visual hallucinations	53	9.5%	37	9.3%	16	10.1%	0.79	–	–	–	–
Cenesthetic hallucinations	76	13.9%	56	14.3%	20	13%	0.69	–	–	–	–
Blunted affect	**284**	**56.2%**	**186**	**51.2%**	**98**	**69.0%**	**<0.0001**	**1.7**	**1.1**	**1.7**	**0.04**
Alogia	148	29.5%	102	28.5%	46	31.9%	0.44	–	–	–	–
Avolia	**269**	**53.5%**	**174**	**48.6%**	**95**	**65.5%**	**<0.0001**	**1.8**	**1.1**	**1.8**	**0.02**
Treatments and side-effects											
SGA	552	90.6%	395	91.0%	157	89.7%	0.62	–	–	–	–
FGA	159	26.1%	100	23.0%	59	33.7%	0.007	1.3	0.7	1.3	0.32
Extrapyramidal symptoms	4.00	7.579	3.63	6.821	4.91	9.125	0.07	0.9	0.5	0.9	0.84
Benzodiazepine	**174**	**28.4%**	**105**	**24.0%**	**69**	**39.4%**	**<0.0001**	**1.8**	**1.1**	**1.8**	**0.02**
Mood stabilisers	110	18.0%	80	18.4%	30	17.1%	0.71	–	–	–	–
Lithium	20	3.3%	16	2.6%	4	0.7%	0.38	–	–	–	–
Valproate	74	12.1%	54	8.9%	20	11.4%	0.74	–	–	–	–
Lamotrigine	11	1.8%	6	1.0%	5	0.8%	0.22	–	–	–	–
Anticholinergic drugs	121	19.8%	82	18.9%	39	22.3%	0.34	–	–	–	–

Clinical, addictive and treatment characteristics in a sample of 613 community-dwelling patients with stabilised schizophrenia. Univariate and multivariate analyses. Significant associations are in bold.
FGA, first-generation antipsychotic; MDD, major depressive disorder; SGA, second-generation antipsychotic.
a. As the Positive and Negative Syndrome Scale is not suited to differentiate the different delusions and hallucination, delusions hallucinations and negative symptoms were evaluated by the Structured Clinical Interview for Mental Disorders v1.0, as well as current cannabis and alcohol misuse disorder.

best way to evaluate depression and antidepressant response in schizophrenia.

Paranoid delusions were associated with both MDD and non-remitted MDD in the present study, contrary to mystic delusion or hallucinations. In our sample, 63% of patients with MDD had current paranoid delusions at the time of the evaluation compared with 42.5% of those without MDD ($P < 0.0001$). Paranoid delusions and depression have both been associated with increased risk of suicide in schizophrenia.[25] This association may be explained by the cognitive biases associated with both paranoid delusions and depression. In one previous study, participants with persecutory delusions were found to be less likely than both healthy participants and participants with depression to report criticising themselves for self-corrective reasons.[26] Hateful self-attacking, reduced self-reassurance and reduced self-corrective self-criticism may be involved in the development or maintenance of persecutory delusions.[26] Paranoia is driven by negative emotions and reductions of self-esteem, rather than serving an immediate defensive function against these emotions and low self-esteem.[27] In a prospective study, depression was found in 30 out of 60 (50%) of the participants with schizophrenia and paranoid delusions, and predicted the maintenance of paranoid delusions over 6 months.[3] Negative cognition has been found to be associated with the maintenance of paranoid delusions in two other studies.[28,29] Future studies of the FACE-SZ cohort follow-up should determine if MDD at baseline is predictive of paranoid delusions maintenance at 1-year follow-up. In cases of non-response to pharmacological treatment, some therapies have shown effectiveness in improving paranoia or MDD in patients with schizophrenia. Cognitive and behavioural therapy has shown effectiveness to reduce negative cognitions about the self, associated with paranoid delusions, and enhance self-confidence.[30] Preliminary data suggests that meta-cognitive therapy may be particularly useful in patients with schizophrenia with resistant MDD.[31]

To our knowledge, this is the first study to show that alcohol misuse disorder is associated with non-response to antidepressant treatment. This result is consistent with the findings of a recent meta-analysis suggesting that antidepressants may be moderately effective in patients with MDD and comorbid alcohol misuse disorder.[32] Another meta-analysis has suggested that alcohol abstinence was the best predictor of MDD remission in non-schizophrenic populations.[33] A recent 4-year follow-up study has shown that alcohol consumption is a risk factor for MDD onset in men.[34] Depression has also been found to maintain alcohol consumption through shame.[35] Alcohol misuse disorder may therefore be seen as a cause as well as a consequence of unremitted MDD. Current alcohol misuse disorder was identified in 5.9% of our sample, which is slightly lower than the mean of 9.4% found in a

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Table 2 Comparison between resistant major depressive disorder (MDD) and responders in a sample of stabilised community-dwelling out-patients with schizophrenia

	Antidepressant treatment (*n* = 204)		Non-remitted MDD (*n* = 90, 44.1%)		Remitted MDD (*n* = 114, 55.9%)		Univariate *P* value	Odds Ratio	95% CI		Adjusted *P* value
	N or mean	(% or s.d.)	*N* or mean	(% or s.d.)	*N* or mean	(% or s.d.)					
Sociodemographic and illness variables											
Gender (male)	55	27.0%	24	43.6%	31	27.2%	0.94	–	–	–	–
Age (years)	34.3	10.3	34.9	11.0	33.8	9.8	0.55	1.0	0.9	1.0	0.53
Education level (years)	12.3	2.8	12.4	2.8	12.2	2.7	0.44	–	–	–	–
Illness duration (years)	11.9	8.7	12.3	8.8	11.5	8.6	0.50	–	–	–	–
Clinical symptoms											
Paranoid delusion	**81**	**52.9%**	**44**	**64.7%**	**37**	**43.5%**	**0.009**	**2.3**	**1.1**	**4.5**	**0.01**
Auditory hallucinations	48	27.0%	21	27.3%	27	26.7%	0.94	–	–	–	–
Visual hallucinations	18	9.7%	9	10.8%	9	8.7%	0.63	–	–	–	–
Cenesthetic hallucinations	23	12.4%	9	11%	14	13.5%	0.61	–	–	–	–
Blunted affect	105	63.3%	50	67.6%	55	59.8%	0.30	–	–	–	–
Alogia	51	29.7%	23	29.5%	28	29.8%	0.96	–	–	–	–
Avolition	102	61.4%	50	67.6%	52	56.5%	0.15	1.7	0.8	3.6	0.1
Addiction											
Current cannabis misuse disorder	8	3.9%	5	5.6%	3	2.6%	0.31	–	–	–	–
Current alcohol misuse disorder	**16**	**7.8%**	**11**	**12.2%**	**5**	**4.4%**	**0.04**	**4.8**	**1.1**	**19.3**	**0.02**
Current daily tobacco smoking	104	53.1%	49	55.7%	55	50.9%	0.51	–	–	–	–
Treatments											
Second-generation antipsychotics	182	91.0%	83	92.2%	99	90.0%	0.59	–	–	–	–
First-generation antipsychotics	53	26.5%	29	32.2%	24	21.8%	0.09	1.3	0.6	3.0	0.40
Extrapyramidal symptoms	0.26	0.3	0.2	0.3	0.2	0.3	0.44	–	–	–	–
Benzodiazepine	83	40.7%	42	46.7%	41	36%	0.12	1.3	0.6	2.8	0.41
Mood stabilisers	30	14.9%	14	15.6%	16	14.4%	0.82	–	–	–	–
Lithium	4	2.0%	1	1.1%	3	2.7%	0.42	–	–	–	–
Valproate	22	10.9%	10	11.1%	12	10.8%	0.94	–	–	–	–
Lamotrigine	4	2.0%	3	3.3%	1	0.9%	0.22	–	–	–	–
Anticholinergic drugs	49	24.4%	24	26.7%	25	22.5%	0.50	–	–	–	–

Response was defined by a Calgary depression scale score <6 and current antidepressant treatment at the time of evaluation. Treatments were unchanged for at least 8 weeks at inclusion. As the Positive and Negative Syndrome Scale is not suited to differentiate the different delusions and hallucinations, delusions hallucinations and negative symptoms were evaluated by the Structured Clinical Interview for Mental Disorders v1.0, as well as current cannabis and alcohol misuse disorder. Significant associations are in bold.

meta-analysis published in 2009.[36] This meta-analysis stipulated that there might be a descending trend in alcohol misuse disorder prevalence in patients with schizophrenia.[36] No previous data in the French schizophrenic population is available to date.

MDD was associated with MetS in the present study. This is consistent with the findings of three other studies carried out in different countries that found the same association.[37–39] There is evidence supporting a pathological predisposition to MetS in both schizophrenia and MDD (for review see Kucerova *et al.*[40]) and the association is currently considered as bidirectional. Altogether, the present findings combined with those of the literature suggest that MetS may play a potential role in the MDD onset and/or maintenance in patients with schizophrenia, this should be confirmed in future studies.

Antidepressants were associated with lower depressive symptoms level in the present study. Although the effectiveness of antidepressant cannot be directly concluded from the present cross-sectional results, these findings can be considered in favour of the effectiveness of antidepressants in patients with schizophrenia that has been suggested in two recent meta-analyses.[9,10] Consistent with the results of these meta-analyses, no antidepressant class was associated with higher or lower depressive symptoms in the present sample. Almost 40% of patients with MDD were treated with benzodiazepine. Benzodiazepine are usually used to treat anxiety and sleep disorders.[41] The benefit of the long-term association of antidepressants and benzodiazepine has been highly debated, with some studies suggesting an adverse long-term effect of benzodiazepine consumption by counteracting antidepressant neurogenesis.[42,43] Benzodiazepine long-term administration may also have other side-effects in patients with schizophrenia, including impaired working memory and higher aggressiveness.[44,45] Although buspirone, a 5HT1A agonist, has been suggested as a potential effective antidepressant augmentation strategy,[46] only two patients in our sample received buspirone (one with current MDD and one without).

We found no association between extrapyramidal symptoms and MDD or response to antidepressants, which is not in favour of the hypothesis of an iatrogenic effect of antipsychotic treatments. Contrary to the non-schizophrenic population, no gender effect was found in the present study, which suggests that MDD is not influenced by hormonal factors in patients with schizophrenia despite recent works on oestrogen influence in schizophrenia pathogenesis and maintenance.[47] We found no association between daily tobacco smoking and MDD in our sample, contrary to the non-schizophrenic population.[48] This may suggest a specific pattern of smoking behaviour related to specific N-Acetylcholine Receptor (NAchR) variants in patients with schizophrenia (for review see Parikh *et al.*[49]). We found no association of MDD with peripheral inflammation.

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Inconsistent results on this point were found in previous studies carried out in similar samples with lower size.[12,13] Several factors may explain this discrepancy: the inclusion of stabilised versus acute-phase patients, the absence of consensual cut-off, the use of high-sensitivity CRP (and not interluekin-6) as a peripheral marker of inflammation, the different antidepressant class administration and the different risk factors for inflammation, including MetS, tobacco smoking, physical activity and diet.

Limits and perspectives

Our results should be taken with caution. As our study has a cross-sectional design, no causal link can be definitely inferred. The number of previous antidepressant treatments was not reported. Other prognosis factors including age at first depressive episode, age at first antidepressant treatment/duration of untreated depression, number of lifetime depressive episodes and lifetime duration of depression should also be included in future studies. Long depressive illness duration and the number of depressive episodes may affect the response to antidepressants. Our sample may not be representative of all patients with schizophrenia, particularly because institutionalised, admitted to hospital or very disabled patients (making thorough assessment difficult) were not referred to the Expert Centers. Sleep disorders, physical activity and vitamin D blood levels may help to explain the resistance to antidepressant treatments, as well as daily dietary intake and microbiota disturbances, and should be explored in further studies. Add-on complementary agents, including omega 3, vitamin D, zinc, *S*-adenosyl methionine, *N*-acetyl cysteine and methylfolate, may also be useful in the treatment of MDD in schizophrenia and should be further explored.[50–52]

Strengths

To the best of our knowledge, the present sample was the largest of all studies exploring MDD in community-dwelling patients with stabilised schizophrenia. This sample size allows the exploration of the factors associated with resistant MDD, which has been done for the first time in an ecological community-dwelling sample of out-patients with stabilised schizophrenia. The use of homogenous and exhaustive standardised diagnostic protocols across the Expert Centers and inclusion of a large number of potential confounding factors in the multivariate analysis (sociodemographic variables, psychotic symptoms, addictive behaviours and detailed treatments) may be considered as strengths of this work. The use of a specific depression scale is also another strength, as well as the exploration of specific symptoms rather than global positive/negative symptoms scores. The national multicentric sample of patients with schizophrenia referred to the Expert Centers may be underscored as another strength.

In summary, combined with the literature, our findings suggest that MDD is frequent in community-dwelling patients with schizophrenia. Antidepressants are associated with lower depressive symptoms level, however a high proportion of patients remain depressed despite treatment. Paranoid delusion and alcohol misuse disorder should be specifically explored in non-remitted patients with schizophrenia with comorbid MDD. These findings should be confirmed in interventional studies.

Guillaume Fond, MD, PhD, **Laurent Boyer**, MD, PhD, Fondation FondaMental, Créteil, France and Faculté de Médecine, Aix-Marseille Université, Centre d'Etude et de Recherche sur les Services de Santé et la Qualité de vie, France; **Fabrice Berna**, MD, PhD, Fondation FondaMental, Créteil, France and INSERM U1114, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Fédération de Médecine Translationnelle de Strasbourg, France; **Ophélia Godin**, PhD, Fondation FondaMental, Créteil, France and UMR_S 1136, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, l'université Pierre et Marie Curie, Sorbonne Universités, France; **Ewa Bulzacka**, MSc, **Méja Andrianarisoa**, MD, **Lore Brunel**, MSc, Fondation FondaMental, Créteil, France and INSERM U955, Université Paris-Est Créteil, Pôle de Psychiatrie des Hôpitaux Universitaires H Mondor, France; **Bruno Aouizerate**, MD, PhD, Fondation FondaMental, Créteil, France, Centre Hospitalier Charles Perrens, Université de Bordeaux, France and INRA, NutriNeuro, University of Bordeaux, France; **Delphine Capdevielle**, MD, PhD, Fondation FondaMental, Créteil, France and INSERM 1061, Service Universitaire de Psychiatrie Adulte, Hôpital la Colombière, CHRU Montpellier, Université Montpellier 1, France; **Isabelle Chereau**, MD, Fondation FondaMental, Créteil, France and CMP B, CHU, EA 7280 Faculté de Médecine, Université d'Auvergne, France; **Nathalie Coulon**, MD, Fondation FondaMental, Créteil, France and INSERM U955, Université Paris-Est Créteil, Pôle de Psychiatrie des Hôpitaux Universitaires H Mondor, France; **Thierry D'Amato**, MD, PhD, Fondation FondaMental, Créteil, France and INSERM U1028, CNRS UMR5292, Centre de Recherche en Neurosciences de Lyon, Université Claude Bernard Lyon 1, Equipe PSYR2, Centre Hospitalier Le Vinatier, France; **Caroline Dubertret**, MD, PhD, Fondation FondaMental, Créteil, France, AP-HP, Department of Psychiatry, Louis Mourier Hospital, Colombes, France and INSERM U894, Faculté de médecine, Université Paris Diderot, Sorbonne Paris Cité, France; **Julien Dubreucq**, MD, Fondation FondaMental, Créteil, France and Centre Référent de Réhabilitation Psychosociale, CH Alpes Isère, France; **Catherine Faget**, MD, Fondation FondaMental, Créteil, France and Faculté de Médecine, Aix-Marseille Université, Centre d'Etude et de Recherche sur les Services de Santé et la Qualité de vie, France; **Sylvain Leignier**, MSc, Fondation FondaMental, Créteil, France and Centre Référent de Réhabilitation Psychosociale, CH Alpes Isère, France; **Christophe Lançon**, MD, PhD, Fondation FondaMental, Créteil, France and Faculté de Médecine, Aix-Marseille Université, Centre d'Etude et de Recherche sur les Services de Santé et la Qualité de vie, France; **Jasmina Mallet**, MD, PhD, Fondation FondaMental, Créteil, France, AP-HP, Department of Psychiatry, Louis Mourier Hospital, Colombes, France and INSERM U894, Faculté de médecine, Université Paris Diderot, Sorbonne Paris Cité, France; **David Misdrahi**, MD, Fondation FondaMental, Créteil, France, Centre Hospitalier Charles Perrens, Université de Bordeaux, France and CNRS UMR 5287, Institut de Neurosciences cognitives et intégratives d'Aquitaine, Université de Bordeaux, France; **Christine Passerieux**, MD, PhD, Fondation FondaMental, Créteil, France and Centre Hospitalier de Versailles, Service de psychiatrie et d'addictologie adulte, Le Chesnay, EA 4047 HANDIReSP, UFR des Sciences de la Santé Simone Veil, Université Versailles Saint-Quentin-en-Yvelines, France; **Romain Rey**, MD, Fondation FondaMental, Créteil, France and INSERM U1028, CNRS UMR5292, Centre de Recherche en Neurosciences de Lyon, Université Claude Bernard Lyon 1, Equipe PSYR2, Centre Hospitalier Le Vinatier, France; **Aurélie Schandrin**, MD, Fondation FondaMental, Créteil, France and INSERM 1061, Service Universitaire de Psychiatrie Adulte, Hôpital la Colombière, CHRU Montpellier, Université Montpellier 1, France; **Mathieu Urbach**, MD, Fondation FondaMental, Créteil, France and Centre Hospitalier de Versailles, Service de psychiatrie et d'addictologie adulte, Le Chesnay, EA 4047 HANDIReSP, UFR des Sciences de la Santé Simone Veil, Université Versailles Saint-Quentin-en-Yvelines, France; **Pierre Vidailhet**, MD, PhD, INSERM U1114, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Fédération de Médecine Translationnelle de Strasbourg, France; **Marion Leboyer**, MD, PhD, **Franck Schürhoff**, MD, PhD, Fondation FondaMental, Créteil, France and INSERM U955, Université Paris-Est Créteil, Pôle de Psychiatrie des Hôpitaux Universitaires H Mondor, France; **Pierre-Michel Llorca**, MD, PhD, Fondation FondaMental, Créteil, France and CMP B, CHU, EA 7280 Faculté de Médecine, Université d'Auvergne, France

Correspondence: Guillaume Fond, MD, PhD, Aix-Marseille Universite, Faculté de Médecine - Secteur Timone, EA 3279: Centre d'Etude et de Recherche sur les Services de Santé et la Qualité de vie, 27 Boulevard Jean Moulin, 13005 Marseille, France. Email: guillaume.fond@ap-hm.fr

First received 13 Feb 2018, final revision 3 Apr 2018, accepted 4 Apr 2018

Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2018.87.

Funding

This work was funded by Assistance Publique des Hôpitaux de Paris, Fondation FondaMental (RTRS Réseau Thématique de Recherche et de Soins Santé Mentale), by the Investissements d'Avenir programme managed by the ANR Agence Nationale de la Recherche (reference no. ANR-11-IDEX-0004-02 and ANR-10-COHO-10-01) and by the Institut National de la Santé et de la Recherche Médicale.

Acknowledgements

We thank the nurses and the patients who were included in the study. We thank Hakim Laouamri and his team (Stéphane Beaufort, Seif Ben Salem, Karmène Souyris, Victor Barteau and Mohamed Laaidi) for the development of the FACE-SZ computer interface, data management, quality control and regulatory aspects. We also thank George Anderson for editorial assistance.

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https://doi.org/10.1192/bjp.2018.87 Published online by Cambridge University Press