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► **To cite this version:**

Nicolas Hoertel, Claire Jaffré, Rachel Pascal de Raykeer, Kibby McMahon, Sarah Barrière, et al.. Subsyndromal and syndromal depressive symptoms among older adults with schizophrenia spectrum disorder: Prevalence and associated factors in a multicenter study. *Journal of Affective Disorders*, 2019, 251, pp.60-70. 10.1016/j.jad.2019.03.007 . hal-02483788

HAL Id: hal-02483788

<https://hal.science/hal-02483788>

Submitted on 14 Aug 2020

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Subsyndromal and syndromal depressive symptoms among older adults with schizophrenia spectrum disorder: Prevalence and associated factors in a multicenter study

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Background: Few studies have examined the prevalence and correlates of subsyndromal and syndromal depressive symptoms (SSSD) among older adults with schizophrenia spectrum disorder. In this report, we examined the prevalence of SSSD and their associations with sociodemographic characteristics, clinical characteristics of schizophrenia, comorbidity, psychotropic medications, quality of life, functioning and mental health care utilization in a large, multicenter sample of older adults with schizophrenia spectrum disorder.

Methods: Data from the Cohort of individuals with Schizophrenia Aged 55 years or more (CSA) were used to examine the prevalence of SSSD, defined using the Center of Epidemiologic Studies Depression (CESD) scale. Clinical characteristics associated with SSSD were explored.

Results: Among 343 older adults with schizophrenia spectrum disorder, 78.1% had either subsyndromal (30.6%) or syndromal (47.5%) depressive symptoms. SSSD were independently associated with positive and negative symptoms, lower quality of life, non-late-onset psychosis, benzodiazepine use and urbanicity. There were no significant associations of SSSD with other sociodemographic characteristics and psychotropic medications, or with general medical conditions. We found no significant differences in the proportion of participants who were treated with antidepressants between those with syndromal depressive symptoms and those without depression (22.1% vs. 20.0%, $p = 0.89$). SSSD were not associated with higher mental health care utilization.

Limitations: Data were cross-sectional and depression was not evaluated with a semi-structured interview.

Conclusion: SSSD may be highly prevalent and under-assessed and/or undertreated among older adults with schizophrenia spectrum disorder. Our findings should alert clinicians about the need to assess systematically and regularly depression in this vulnerable population.

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1. Introduction

Due to the ageing of the general population in Western countries, the number of people with schizophrenia who are at least 55 years old is rapidly increasing and is expected to reach almost a quarter of the United States population diagnosed with schizophrenia by 2025 (Cohen et al., 2008). Depression is commonly comorbid during the course of schizophrenia. 24% to 48% of older adults with schizophrenia spectrum disorder suffer from syndromal depressive symptoms (Cohen and Ryu, 2015; Diwan et al., 2007; Meesters et al., 2014), and up to 75% of them would suffer from syndromal or subsyndromal depressive symptoms (SSSD) (Cohen et al., 2015). SSSD are associated with the increase in symptoms of schizophrenia (Cohen, 1995; Cohen et al., 1996; Heila et al., 1997; Jin et al., 2001; Johnson, 1988; Roy, 1981; Zisook et al., 1999; 2007), poorer functional remission (Cohen et al., 2015; Diwan et al., 2007; Limosin, 2009; Meesters et al., 2014; Wetherell et al., 2003), increased risk of suicide (Zisook et al., 2007) and lower quality of life (Cohen et al., 2017; Diwan et al., 2007; Jin et al., 2001; Patterson et al., 1997) among older adults with schizophrenia. Despite the common comorbidity between depression and schizophrenia among older adults and its debilitating consequences, few studies have examined the prevalence of SSSD and their related characteristics among older adults with schizophrenia spectrum disorder (Cohen et al., 2015). Such knowledge would help mental health professionals prevent, detect and manage this often underdiagnosed comorbidity in this population (Zisook et al., 1999).

Prior research has yielded conflicting evidence on the role of sociodemographic characteristics, psychiatric and other medical conditions and psychotropic medications in the risk of depression among older adults with schizophrenia. Some studies have identified multiple factors associated with depressive symptoms in this population, such as younger age (Cohen and Ryu, 2015; Cohen et al., 1996), psychiatric comorbidity (Zisook et al., 1999; Zisook et al., 2007), general medical comorbidity (Diwan et al., 2007; Meesters et al., 2014), and greater number of psychotropic medications (Cohen and Ryu, 2015). On the other hand, other studies did not find a significant impact of these factors, including age (Diwan et al., 2007; Zisook et al., 1999), psychiatric comorbidity (Meesters et al., 2014; Zisook et al., 2007), general medical comorbidity (Cohen and Ryu, 2015; Zisook et al., 1999) and the number and the dose of antipsychotics (Zisook et al., 1999; Zisook et al., 2006). However, this previous research had limited statistical power, as most studies relied on relatively small samples ranging from 60 to 198 older adults with schizophrenia (Cohen and Ryu, 2015; Cohen et al., 1996; Meesters et al., 2014; Zisook et al., 1999; Zisook et al., 2006). Additionally, prior studies were conducted in only three sites (Cohen and Ryu, 2015; Diwan et al., 2007; Meesters et al., 2014; Zisook et al., 2007, 2006, 1999), limiting the generalizability of their findings. Therefore, research using larger samples of older adults with schizophrenia from multiple sites may provide a better knowledge of clinical factors associated with SSSD and improve their early recognition and treatment in this vulnerable population.

To address this gap in the literature, we used data drawn from a large ($n = 353$) study conducted at 63 centers in France, the “Cohort of individuals with Schizophrenia Aged 55 years or more” (CSA), and examined the prevalence and potential associations of SSSD with sociodemographic and clinical characteristics, comorbidity, quality of life, functioning, psychotropic medications and mental health care utilization.

2. Methods

2.1. Sample

Data were drawn from the CSA study, a cohort of 353 inpatients (34.1%) or outpatients (65.9%) aged 55 years or more with schizophrenia spectrum disorder, which included people with an

International Classification of Diseases, Tenth edition (ICD-10) diagnosis of schizophrenia (82.4%) or schizoaffective disorder (17.6%). Participants were recruited between February 2010 and June 2013 from French state hospital psychiatric departments that covered 63 mutually independent catchment areas (Raucher-Chéné et al., 2015). Exclusion criteria included having limited French proficiency, being not affiliated to the social security system, meeting ICD-10 criteria for any pervasive developmental disorder or major neurocognitive disorder, and having any neurological disorder affecting the central nervous system or any serious, life threatening medical or surgical condition that requires immediate treatment. Each participant was interviewed face-to-face by his/her treating psychiatrist, who collected all clinical data. The research protocol, including informed consent procedures, was conducted in accordance with the Declaration of Helsinki ethical guidelines, and received full ethical review and approval from the local research ethics committee, the Advisory Committee on Information Processing in Material Research in the Field of Health and the National Board on Computerized Information and Freedoms.

2.2. Measures

2.2.1. Assessment of schizophrenia spectrum disorder

Diagnoses of schizophrenia and schizoaffective disorder were assessed face-to-face by psychiatrists using ICD-10 criteria. Age at onset of first psychotic symptoms was retrospectively investigated and categorized as non-late-onset (i.e. before 40 years), late-onset (i.e. between 40 and 60 years) and very-late onset (i.e. after 60 years) according to prior recommendation (Howard et al., 2000), and the duration of the disorder was estimated.

2.2.2. Assessment of subsyndromal and syndromal depressive symptoms (SSSD)

SSSD over the past week were self-reported by participants using the Center of Epidemiologic Studies Depression scale (CES-D) (Radloff, 1977) and categorized as follows: (1) no depression ($CES-D \leq 7$), (2) subsyndromal depression ($CES-D = 8-15$) and (3) syndromal depression ($CES-D \geq 16$) (Camacho et al., 2014). Respondents were asked to indicate on a scale from 0 (rarely or none of the time) to 3 (most of the time) how often they experience 20 symptoms related to depression (e.g., I felt everything I did was an effort). This questionnaire has been designed for use in community studies (Airagnes et al., 2016b; Matta et al., 2019; Radloff, 1977; Roy, 1981) and validated in adult samples of all ages with psychiatric disorders (Irwin et al., 1999; Shafer, 2006), including adults with schizophrenia spectrum disorder (Herniman et al., 2017). In our study, internal consistency reliability of the CES-D scale was acceptable, with Cronbach's alpha = 0.72.

2.2.3. Sociodemographic characteristics

Sociodemographic characteristics included gender, age, education, marital status, parenthood and urbanicity (defined as living in an area comprising more than 1000 inhabitants per km²).

2.2.4. Assessment of psychiatric symptoms, alcohol and nicotine consumption and suicide attempts

We used the 18-item version of the Brief Psychiatric Rating Scale (BPRS) (Overall, 1962; Leucht et al., 2005), a widely used instrument for assessing psychiatric symptoms in individuals with schizophrenia spectrum disorder. Each symptom is rated from 1 (absence) to 7 (severe). We examined the total score and the 5 subscale scores (Shafer, 2005): 1) Affect (anxiety, guilt, depression, somatic); 2) Positive Symptoms (thought content, conceptual disorganization, hallucinatory behavior, grandiosity); 3) Negative Symptoms (blunted affect, emotional withdrawal, motor retardation); 4) Resistance (hostility, uncooperativeness, suspiciousness); and 5) Activation (excitement, tension, mannerisms-posturing). In our study, internal consistency reliability of the BPRS scale was good, with Cronbach's alpha = 0.85.

Current smoking status was recorded. At-risk alcohol consumption was evaluated using the CAGE questionnaire (Ewing, 1984; Kitchens, 1994). All participants were also asked whether they ever attempted suicide and whether they attempted suicide during the year preceding the interview.

2.2.5. Psychotropic medications

All psychotropic medications prescribed at the time of the interview were recorded, and in particular antipsychotics, antidepressants, benzodiazepines and anticholinergic antiparkinsonian drugs.

2.2.6. Mental health care utilization

The lifetime number of hospitalizations in a psychiatric department was recorded at the time of the interview.

2.2.7. Medical conditions

The number of comorbid non-psychiatric medical conditions (e.g., cardiovascular disorder, cancer) was recorded for all participants at the time of the interview. Blood pressure and body mass index (BMI) were measured in all participants. Individuals whose systolic blood pressure was >140 mm Hg or diastolic blood pressure >90 mm Hg were considered as having high blood pressure. Based on the recommendation of a recent meta-analysis (Winter et al., 2014) on the association between BMI and all-cause mortality risk in older adults, we categorized BMI as follows: underweight (<23 kg/m²), healthy weight (23–30 kg/m²) and overweight (>30 kg/m²).

Investigators were asked whether the participant had a blood test or an electrocardiogram in the past year, and whether the participant consulted a general practitioner or was hospitalized in a non-psychiatric medical department in the past year.

2.2.8. Overall functioning and cognitive functioning

The Global Assessment of Functioning (GAF) scale (Endicott et al., 1976) was used for evaluating the overall social, occupational, and psychological functioning of participants. Scale scores range from 0 to 100 with higher scores signifying better functioning. Prior studies support the reliability and convergent validity of the GAF scale scores in populations with psychiatric disorders (Jones et al., 1995). The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) was used for evaluating global cognitive impairment. In our study, internal consistency reliability of the GAF and MMSE scores was good (Cronbach's alpha = 0.87 and 0.93, respectively).

2.2.9. Quality of life

We used the Quality of Life Scale (QLS) (Heinrichs et al., 1984), an instrument widely used to assess quality of life in clinical studies of schizophrenia (Lehman, 1996). The QLS has 21 items rated on a 7-point scale from 0 to 6 with descriptive anchors; higher scores reflect higher quality of life (Heinrichs et al., 1984). In our study, internal consistency reliability of the QLS was excellent (Cronbach's alpha = 0.91).

2.3. Missing data

The mean percentage of missing data in the study was 1.2%. Missing data were imputed using Markov chain Monte Carlo (MCMC) methods (Schafer, 1997). All significant results remained significant in sensitivity analyses excluding respondents with missing data.

2.4. Statistical analyses

Percentages and means (\pm SD) were estimated to provide descriptive information on sociodemographic and clinical characteristics, psychiatric and other medical comorbidity, quality of life and overall functioning, psychotropic medications and mental health care utilization in older adults with schizophrenia spectrum disorder according to the presence of depressive symptoms. Subsyndromal and syndromal

depressive symptoms (SSSD) were considered a 3-class categorical variable (i.e., no depression (CES-D score \leq 7), subsyndromal depression (CES-D score: 8–15) and syndromal depression (CES-D \geq 16)). This categorical variable of SSSD was used as the outcome variable and the rest of the variables were used as predictors. Multinomial logistic regression analyses were used to study the univariate associations between SSSD and its potential predictors. Given our relatively large sample, statistical significance was evaluated using a two-sided design with alpha risk set *a priori* at 0.01 to reduce the risk of type I error due to multiple testing. Next, in order to determine whether variables that are significant in univariate analyses and possibly correlated with each other do have independent associations with SSSD, we performed a multivariable multinomial logistic regression analysis that included all variables showing a significant association in univariate analyses (except the BPRS "affect" subscale whom items are substantially associated with the CES-D score (eTable 11)). For all logistic regression models, we examined potential collinearity problem by performing collinearity diagnostics produced by linear regressions with the option tolerance and variance inflation factor (Midi et al., 2010). To have enough statistical power in the multivariable analysis, statistical significance was evaluated using a two-sided design with alpha risk set *a priori* at 0.05. Statistical analyses were performed using PASW Statistics 18 software (IBM Corp., Armonk, NY, USA, released 2009).

2.5. Supplementary analyses

We conducted the same analyses described above, distinguishing between inpatients and outpatients. These supplementary analyses allowed us to evaluate whether there are differences in the prevalence of SSSD between inpatients and outpatients. They also allowed us to examine whether the pattern of associations observed in the full sample holds across these two subpopulations.

3. Results

3.1. Prevalence of depressive symptoms

Among the 353 older participants with schizophrenia or schizoaffective disorder, 10 (2.8%) were excluded from our analyses because data on depression were missing. Out of the 343 remaining participants, 75 (21.9%) had no depression, 105 (30.6%) subsyndromal depressive symptoms, 163 (47.5%) depressive symptoms and 268 (78.1%) either subsyndromal or syndromal depressive symptoms (SSSD).

3.2. Depressive symptoms and sociodemographic and clinical characteristics

Among older participants with schizophrenia spectrum disorder, SSSD were significantly and positively associated with BPRS total score and scores of the 5 subscales of the BPRS (i.e., affect, positive symptoms, negative symptoms, activation and resistance), non-late-onset psychosis and urbanicity (Table 1).

3.3. Depressive symptoms and psychotropic medications

SSSD were significantly associated with benzodiazepine use (Table 2). The proportion of participants with schizophrenia spectrum disorder receiving an antidepressant did not differ statistically across the 3 groups: 20.0% in those with no depression, 20.0% in those with subsyndromal depression and 22.1% in older adults with syndromal depression ($p = 0.89$). There were no significant associations of depressive symptoms with the number of antipsychotics, antipsychotic type (i.e., typical or atypical), or its formulation (oral vs. long-acting injectable formulation).

Table 1

Associations of subsyndromal or syndromal depressive symptoms (SSSD) with sociodemographic and clinical characteristics of schizophrenia in older adults with schizophrenia spectrum disorder ($n = 343$).

	No depression ($n = 75$)	Subsyndromal depression ($n = 105$)	Syndromal depression ($n = 163$)	Syndromal or subsyndromal depression ($n = 268$)	Subsyndromal depression versus No depression	Syndromal depression versus No depression	Syndromal or subsyndromal depression versus No depression
	%	%	%	%	OR [95% CI] ^E	OR [95% CI] ^E	OR [95% CI] ^E
Sociodemographic characteristics							
Gender							
Men	52.0	46.7	49.1	48.1	1.00	1.00	1.00
Women	48.0	53.3	50.9	51.9	1.24 [0.68–2.24]	1.12 [0.65–1.94]	1.17 [0.70–1.95]
Education							
Less than high school	69.9	66.7	71.2	69.4	0.87 [0.39–1.94]	1.30 [0.60–2.84]	1.09 [0.54–2.24]
High school	13.7	15.2	16.0	15.7	1.01 [0.35–2.95]	1.49 [0.54–4.11]	1.26 [0.49–3.24]
College or higher	16.4	18.1	12.9	14.9	1.00	1.00	1.00
Marital status							
Widowed	8.0	12.4	8.6	10.1	2.03 [0.71–5.80]	1.18 [0.43–3.27]	1.48 [0.58–3.81]
Married or as if married	12.0	15.2	17.2	16.4	1.67 [0.67–4.15]	1.57 [0.69–3.61]	1.61 [0.73–3.54]
Divorced or separated	18.7	25.7	18.4	21.3	1.81 [0.85–3.87]	1.08 [0.52–2.24]	1.34 [0.68–2.62]
Never married	61.3	46.7	55.8	52.2	1.00	1.00	1.00
Parenthood							
Urbanicity ^a	37.3	45.7	40.5	42.5	1.41 [0.77–2.59]	1.14 [0.65–2.01]	1.24 [0.73–2.10]
Age	66.7	69.2	84.9	78.7	1.13 [0.60–2.12]	2.81 [1.47–5.37]**	1.85 [1.05–3.25]*
55–64	44.0	31.4	49.7	42.5	0.67 [0.26–1.70]	0.79 [0.35–1.80]	0.75 [0.34–1.65]
65–74	42.7	54.3	31.3	40.3	1.19 [0.48–2.95]	0.51 [0.22–1.19]	0.73 [0.33–1.62]
75+	13.3	14.3	19.0	17.2	1.00	1.00	1.00
Inpatient/outpatient status							
Inpatient	32.0	28.6	38.9	34.8	1.00	1.00	1.00
Outpatient	68.0	71.4	61.1	65.2	1.18 [0.62–2.24]	0.74 [0.41–1.32]	0.65 [0.51–1.52]
Characteristics of schizophrenia							
Age-at-onset							
Non-late-onset (<40y)	69.9	80.8	84.0	82.7	1.00	1.00	1.00
Late-onset (40–60y)	27.4	18.3	12.8	15.0	0.58 [0.28–1.18]	0.39 [0.19–0.78]**	0.46 [0.25–0.86]*
Very late-onset (>60y)	2.7	1.0	3.2	2.3	na	na	na
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	OR [95% CI] ^E	OR [95% CI] ^E	OR [95% CI] ^E
BPRS total score							
Affect	32.3 (9.5)	39.8 (14.0)	49.8 (14.1)	45.9 (14.8)	1.06 [1.03–1.10]***	1.12 [1.09–1.15]***	1.09 [1.06–1.12]***
Positive symptoms	7.1 (3.2)	9.2 (3.6)	12.7 (4.1)	11.3 (4.3)	1.22 [1.10–1.34]***	1.52 [1.37–1.68]***	1.36 [1.24–1.49]***
Negative symptoms	7.2 (3.7)	8.3 (4.5)	10.4 (5.2)	9.6 (5.1)	1.08 [0.99–1.17]	1.19 [1.10–1.28]***	1.15 [1.07–1.23]***
Activation	6.7 (3.5)	8.5 (4.1)	10.0 (4.0)	9.4 (4.1)	1.14 [1.05–1.24]**	1.26 [1.16–1.36]***	1.21 [1.12–1.30]***
Resistance	5.6 (2.7)	6.7 (3.2)	7.4 (3.5)	7.1 (3.4)	1.14 [1.03–1.26]*	1.21 [1.09–1.33]***	1.18 [1.07–1.29]***
Duration of disorder	4.5 (2.1)	5.6 (3.4)	7.3 (3.9)	6.7 (3.8)	1.19 [1.05–1.34]**	1.36 [1.21–1.53]***	1.29 [1.15–1.44]***
	36.2 (13.5)	37.3 (10.9)	38.2 (14.2)	37.9 (13.0)	1.01 [0.98–1.03]	1.01 [0.99–1.03]	1.01 [0.99–1.03]

The CES-D variable was categorized as no depression (CES-D score ≤ 7), subsyndromal depression (CES-D score: 8–15) and syndromal depression (CES-D score ≥ 16).

Estimates in bold are statistically significant (two-sided p -value < 0.01).

Abbreviations: CESD = Center of Epidemiologic Studies Depression scale; OR = odds ratio; CI = confidence interval; na = not applicable; SD = standard deviation.

^a Urbanicity was defined as living in an area comprising more than 1000 inhabitants per km².

^E Odds ratios were obtained using logistic regression models with 'no depression' as reference category.

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.001$.

3.4. Depressive symptoms and general medical conditions

Among older adults with schizophrenia spectrum disorder, we did not find any significant associations between SSSD and physical health features (i.e., BMI, high blood pressure, smoking and at-risk drinking), past-year physical health monitoring (i.e., rates of consultation with a general practitioner and hospitalization in a non-psychiatric department, and proportions of participants who had an electrocardiogram and a blood test in the past year), and the number of general medical conditions (Table 3).

3.5. Depressive symptoms and quality of life and overall functioning

The mean MMSE and GAF total scores were significantly lower in participants with SSSD than in those without depressive symptoms. The mean QLS total score of participants with depressive symptoms was significantly lower than participants without depressive symptoms (49.0 vs. 65.6; $p < 0.001$). History of suicide attempts within the past year was more frequent in participants with depressive symptoms than in their counterparts without depressive symptoms (3.1% vs. 0.0%). There were no significant associations of SSSD with lifetime history of suicide attempts or mental health utilization (Table 4).

Table 2Associations of subsyndromal or syndromal depressive symptoms (SSSD) with **psychotropic medications** in older adults with schizophrenia ($n = 343$).

	No depression ($n = 75$)	Subsyndromal depression ($n = 105$)	Syndromal depression ($n = 163$)	Syndromal or subsyndromal depression ($n = 268$)	Subsyndromal depression versus No depression	Syndromal depression versus No depression	Syndromal or subsyndromal depression versus No depression
	%	%	%	%	OR [95% CI] [‡]	OR [95% CI] [‡]	OR [95% CI] [‡]
Psychotropic medications							
Number of antipsychotics prescribed							
0	8.0	6.7	8.6	7.8	1.02 [0.28–3.77]	0.82 [0.26–2.54]	0.88 [0.30–2.58]
1	73.3	78.1	66.9	71.3	1.31 [0.59–2.89]	0.69 [0.35–1.38]	0.87 [0.45–1.68]
2+	18.7	15.2	24.5	20.9	1.00	1.00	1.00
Atypical antipsychotics	50.7	63.8	61.3	62.3	1.72 [0.94–3.14]	1.55 [0.89–2.68]	1.61 [0.96–2.70]
Typical antipsychotics	49.3	41.0	47.2	44.8	0.71 [0.39–1.29]	0.92 [0.53–1.59]	0.83 [0.50–1.39]
Antipsychotic under long-acting injectable (LAI) formulation	31.1	36.5	29.6	32.3	1.28 [0.68–2.41]	0.93 [0.51–1.70]	1.06 [0.61–1.85]
Antidepressants	20.0	20.0	22.1	21.3	1.00 [0.48–2.10]	1.13 [0.58–2.23]	1.08 [0.57–2.04]
Benzodiazepines	18.7	29.5	35.6	33.2	1.83 [0.89–3.74]	2.41 [1.21–4.67]**	2.17 [1.15–4.08]*
Anticholinergic antiparkinsonian drugs	32.0	27.6	38.0	34.0	0.81 [0.43–1.55]	1.30 [0.73–2.33]	1.09 [0.63–1.89]

The CES-D variable was categorized as no depression (CES-D score ≤ 7), subsyndromal depression (CES-D score: 8–15) and syndromal depression (CES-D score ≥ 16).

Estimates in bold are statistically significant (two-sided p -value < 0.01).

Abbreviations: OR=odds ratio; CI=confidence interval; na=not applicable.

[‡] Odds ratios were obtained using logistic regression models with ‘no depression’ as reference category.

* $p < 0.05$;

** $p < 0.01$;*** $p < 0.001$.

3.6. Depressive symptoms and associated factors

Results from the multivariable multinomial logistic regression analysis with all variables that had a significant association in univariate analyses revealed that positive and negative symptoms, low quality of life, non-late-onset psychosis, benzodiazepine use and urbanicity were significantly and independently associated with SSSD among older adults with schizophrenia spectrum disorder (Table 5).

3.7. Supplementary statistical analyses

Among the 117 inpatients, 24 (20.5%) did not have depressive symptoms, 30 (25.6%) had subsyndromal depressive symptoms, 63 (53.8%) syndromal depressive symptoms and 93 (79.5%) either subsyndromal or syndromal depressive symptoms. Among the 226 outpatients, these rates were respectively 22.6% ($N = 51$), 33.2% ($N = 75$), 44.2% ($N = 100$) and 77.4% ($N = 175$). There were no significant differences in the prevalence of SSSD between these two subpopulations ($p = 0.213$). Among outpatients, we found that SSSD were independently associated with lower quality of life, negative symptoms, resistance and non-late-onset psychosis (eTables 1 to 5), while they were independently associated with higher BPRS total score and lower quality of life among inpatients (eTables 6 to 10).

In all multivariable logistic regressions, the variance inflation factor and tolerance values of each predictor variable were respectively lower than 2.5 and higher than 0.2, supporting that multicollinearity was not a concern in our analyses (Midi et al., 2010) (eTable 12).

4. Discussion

In a large, multicenter sample of older adults with schizophrenia spectrum disorder, we found that 78.1% of older adults had either subsyndromal (30.6%) or syndromal (47.5%) depressive symptoms (SSSD). SSSD were independently associated with positive and negative symptoms, lower quality of life, non-late-onset psychosis, benzodiazepine use and urbanicity, although the magnitudes of these associations were modest. Furthermore, our findings suggest potential differences between inpatients and outpatients in these associations. There were no significant differences in antidepressant prescription rates between

participants with and without SSSD. Finally, SSSD were not significantly associated with other sociodemographic characteristics and other types of psychotropic medications, general medical conditions, and mental health care utilization.

SSSD were highly prevalent among older adults with schizophrenia spectrum disorder in our study. We found that 78.1% of participants had either subsyndromal (30.6%) or syndromal (47.5%) depressive symptoms (SSSD), which is in line with prior studies indicating that 24% to 48% of older with schizophrenia spectrum disorder suffer from syndromal depression (Cohen and Ryu, 2015; Diwan et al., 2007; Meesters et al., 2014) and that up to 75% suffer from subsyndromal or syndromal depression (Cohen et al., 2015). Taking together, these findings support that most older adults with schizophrenia present substantial depressive symptoms.

We found that SSSD among older adults with schizophrenia were independently associated with an increased likelihood of endorsing positive and negative symptoms, lower quality of life, non-late-onset psychosis, benzodiazepine use and urbanicity. In a large, multicenter sample, we confirmed earlier findings that depressive symptoms may be associated with an increase in positive and negative symptoms (Cohen, 1995; Cohen et al., 1996; Heila et al., 1997; Jin et al., 2001; Johnson, 1988; Roy, 1981; Zisook et al., 1999; Zisook et al., 2007) and lower quality of life (Cohen et al., 2017; Diwan et al., 2007; Jin et al., 2001; Patterson et al., 1997) among older adults with schizophrenia spectrum disorder. To our knowledge, this is the first study to demonstrate significant associations between SSSD and benzodiazepine use, non-late onset schizophrenia and urbanicity within a sample of older adults with schizophrenia spectrum disorder. Although benzodiazepine use in older patients is associated with many debilitating side effects that might increase the risk of depression (Airagnes et al., 2016a), this association may mainly reflect a therapeutic strategy that many providers use for older patients with more severe or co-morbid disorders. The association of urbanicity with SSSD in our study is consistent with the well-established effect of urbanicity on risks of schizophrenia and affective disorders in the general population (Eckert and Kohler, 2014; Vassos et al., 2012). We also found a higher prevalence of SSSD in individuals with an onset of schizophrenia spectrum disorder before 40 years of age than in those with an age at onset between 40 and 60 years. This difference was not explained by a significant difference in the proportion of

Table 3
Associations of subsyndromal or syndromal depressive symptoms (SSSD) with **physical health features and monitoring and medical conditions in older participants with schizophrenia (n = 343)**.

	No depression (n = 75)	Subsyndromal depression (n = 105)	Syndromal depression (n = 163)	Syndromal or subsyndromal depression (n = 268)	Subsyndromal depression versus No depression	Syndromal depression versus No depression	Syndromal or subsyndromal depression versus No depression
	%	%	%	%	OR [95% CI] ^f	OR [95% CI] ^f	OR [95% CI] ^f
Past-year physical health monitoring							
At least one consultation with a general practitioner	81.3	77.1	82.2	80.2	0.78 [0.37-1.62]	1.06 [0.52-2.15]	0.93 [0.48-1.79]
At least one electrocardiogram	48.0	48.6	46.0	47.0	1.02 [0.57-1.85]	0.92 [0.53-1.60]	0.96 [0.58-1.61]
At least one blood test	85.3	80.0	73.6	76.1	0.69 [0.31-1.53]	0.48 [0.23-1.00]	0.55 [0.27-1.10]
Hospitalization in a non-psychiatric department	25.3	22.9	19.6	20.9	0.87 [0.44-1.74]	0.72 [0.44-1.17]	0.78 [0.43-1.42]
Physical health features							
BMI^a							
Obesity	25.7	23.8	30.4	27.8	0.96 [0.43-2.12]	1.55 [0.74-3.22]	1.28 [0.65-2.54]
Normal weight	41.9	44.8	44.7	44.7	1.10 [0.55-2.21]	1.39 [0.72-2.69]	1.26 [0.69-2.32]
Malnutrition	32.4	31.4	24.8	27.4	1.00	1.00	1.00
High blood pressure^b	77.3	67.6	68.1	67.9	0.61 [0.31-1.21]	0.63 [0.33-1.18]	0.62 [0.34-1.13]
Current smokers	29.3	28.6	28.2	28.4	0.96 [0.50-1.85]	0.95 [0.52-1.73]	0.95 [0.54-1.68]
At-risk drinking^c	0.0	0.0	2.5	1.5	na	na	na
Medical conditions	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	OR [95% CI] ^f	OR [95% CI] ^f	OR [95% CI] ^f
Number of medical conditions	1.9 (1.4)	2.1 (1.6)	2.3 (1.7)	2.2 (1.6)	1.09 [0.89-1.32]	1.17 [0.98-1.40]	1.14 [0.96-1.35]

The CES-D variable was categorized as no depression (CES-D score ≤ 7), subsyndromal depression (CES-D score: 8-15) and syndromal depression (CES-D score ≥ 16).

Estimates in bold are statistically significant (two-sided p-value < 0.01).

Abbreviations: OR = odds ratio; CI = confidence interval; SD = standard deviation; na = not applicable.

^a Body mass index was defined as body weight (in kg) divided by the square of height (in m). Obesity and malnutrition were defined as having a body mass index > 30 kg/m² and < 23 kg/m², respectively.

^b High blood pressure was defined as having a systolic blood pressure > 140 mm Hg or a diastolic blood pressure > 90 mm Hg.

^c At-risk drinking was defined as having a CAGE test score ≥ 2.

^f Odds ratios were obtained using logistic regression models with 'no depression' as reference category. *p < 0.05; **p < 0.01; ***p < 0.001.

Table 4
Associations of subsyndromal or syndromal depressive symptoms (SSDD) with functioning, quality of life, suicide attempts and mental health care utilization in older adults with schizophrenia (n = 343).

	No depression (n = 75)	Subsyndromal depression (n = 105)	Syndromal depression (n = 163)	Syndromal or subsyndromal depression (n = 268)	Subsyndromal depression versus No depression	Syndromal depression versus No depression	Syndromal or subsyndromal depression versus No depression
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	OR [95% CI] [£]	OR [95% CI] [£]	OR [95% CI] [£]
Functioning							
GAF total score	53.7 (16.9)	49.3 (17.4)	44.8 (14.8)	46.6 (16.0)	0.98 [0.97-1.01]	0.97 [0.95-0.98] ***	0.97 [0.96-0.99] **
MMSE total score	24.4 (4.4)	23.9 (4.8)	22.6 (5.4)	23.1 (5.1)	0.98 [0.92-1.05]	0.93 [0.87-0.98]	0.95 [0.90-0.99] [£]
Quality of life							
QLS total score	65.6 (19.3)	54.9 (20.9)	45.0 (17.5)	49.0 (19.5)	0.98 [0.96-0.99] **	0.95 [0.93-0.97] ***	0.96 [0.95-0.98] ***
Suicide attempts							
Lifetime history of suicide attempts	29.3	22.9	%	%	OR [95% CI] [£]	OR [95% CI] [£]	OR [95% CI] [£]
Past-year history of suicide attempts	0.0	0.0	2.5	1.5	0.71 [0.36-1.40]	1.07 [0.59-1.94]	0.92 [0.52-1.62]
Mental health utilization							
Lifetime number of hospitalizations in a psychiatric department attempts	50.7	49.5	41.1	44.4	na	na	na
0-4	32.0	26.7	28.8	28.0	0.71 [0.32-1.57]	0.47 [0.23-1.00]	0.55 [0.28-1.10]
5-10	17.3	23.8	30.1	27.6	0.61 [0.26-1.44]	0.52 [0.24-1.14]	0.55 [0.26-1.16]
> 10					1.00	1.00	1.00

The CES-D variable was categorized as no depression (CES-D score ≤ 7), subsyndromal depression (CES-D score: 8-15) and syndromal depression (CES-D score ≥ 16).

Estimates in bold are statistically significant (two-sided p-value < 0.01).

Abbreviations: OR = odds ratio; CI = confidence interval; GAF = Global Assessment of functioning; MMSE = Mini Mental State Examination; QLS = Quality of Life Scale; SD = standard deviation; na = not applicable.

[£] Odds ratios were obtained using logistic regression models with 'no depression' as reference category.

* p < 0.05;

** p < 0.01;

*** p < 0.001.

Table 5

Multivariable logistic regression analyses of factors showing significant univariate associations with subsyndromal or syndromal depressive symptoms (SSSD) in older adults with schizophrenia ($n = 343$).

	Subsyndromal depression versus No depression	Syndromal depression versus No depression	Syndromal or subsyndromal depression versus No depression
	AOR [95% CI] / p-value [£]	AOR [95% CI] / p-value [£]	AOR [95% CI] / p-value [£]
Urbanicity	1.55 [0.62–3.87] / 0.344	6.89 [2.28–20.87] / 0.001	2.53 [1.06–6.02] / 0.037
Age-at-onset of schizophrenia			
Non-late-onset (< 40y)	1.00	1.00	1.00
Late-onset (40–60y)	0.42 [0.14–1.25] / 0.120	0.25 [0.07–0.85] / 0.027	0.35 [0.13–0.99] / 0.049
Very late-onset (> 60y)	na	na	na
Positive symptoms	1.02 [0.88–1.17] / 0.835	1.18 [1.02–1.38] / 0.031	1.07 [0.94–1.22] / 0.312
Negative symptoms	1.14 [0.99–1.30] / 0.071	1.22 [1.05–1.41] / 0.008	1.17 [1.02–1.33] / 0.023
Activation	1.02 [0.86–1.22] / 0.823	0.86 [0.70–1.05] / 0.129	0.97 [0.82–1.15] / 0.713
Resistance	1.12 [0.91–1.38] / 0.268	1.17 [0.95–1.45] / 0.141	1.14 [0.94–1.40] / 0.187
Benzodiazepines	1.59 [0.59–4.30] / 0.358	3.42 [1.19–9.86] / 0.023	2.09 [0.82–5.32] / 0.123
GAF total score	1.00 [0.97–1.04] / 0.859	1.02 [0.98–1.06] / 0.338	1.01 [0.98–1.04] / 0.592
QLS total score	0.98 [0.95–1.01] / 0.114	0.96 [0.93–0.98] / 0.002	0.97 [0.95–0.99] / 0.012

The CES-D variable was categorized as no depression (CES-D score ≤ 7), subsyndromal depression (CES-D score: 8–15) and syndromal depression (CES-D score ≥ 16).

Estimates in bold are statistically significant (two-sided p-value < 0.05).

Abbreviations: AOR = adjusted odds ratio; CI = confidence interval; GAF = Global Assessment of functioning; QLS = Quality of Life Scale; na = not applicable.

[£] Odds ratios were obtained using logistic regression models with ‘no depression’ as reference category and were adjusted for all other variables (df = 11).

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

individuals with schizoaffective disorder between these 2 groups (16.9% vs. 23.0%, respectively, $p = 0.51$). Although the duration of schizophrenia spectrum disorder was not significantly associated with SSSD, this difference in the prevalence of SSSD may result from a longer exposition to schizophrenia spectrum disorder and its negative functional consequences or might reflect a true clinical difference, which might support the view that late-onset schizophrenia spectrum disorder could be a distinct subtype of schizophrenia (Howard et al., 2000; Maglione et al., 2014). However, this finding was only significant when considering the full sample of inpatients and outpatients, suggesting the need of other studies to confirm this result.

Although we did not find any significant difference in the prevalence of SSSD between inpatients and outpatients, there were substantial differences in the associations between depressive symptoms and psychiatric symptoms, quality of life, and age at onset of psychosis between these two groups. Among outpatients, SSSD were independently associated with negative symptoms, resistance, lower quality of life and non-late-onset psychosis. On the other hand, SSSD were independently associated with higher psychiatric symptoms, assessed with the BPRS total score, and lower quality of life among inpatients. These differences should be interpreted with caution given the relatively low proportion of inpatients in our study ($N = 117$), which may have limited the statistical power. However, our results support that SSSD are associated with an increased likelihood of endorsing symptoms of schizophrenia and may play an important role in the quality of life of older adults with schizophrenia spectrum disorder. These findings suggest that treating depression in this population may have a broad range of benefits such as reducing the suffering of these patients, decreasing the burden of suicide and improving their quality of life (Hoertel et al., 2018, 2015a; Kasckow et al., 2010; Pascal de Raykeer et al., 2018; Sheline et al., 2006; Vulser et al., 2018; Zisook et al., 2009).

We found no significant differences in antidepressant prescription rates between participants with and without SSSD. We found that 22.1% of participants with syndromal depressive symptoms were prescribed an antidepressant medication. This proportion is similar to what has been observed in a nationally representative sample of individuals with schizophrenia who have had office visits with outpatient physicians (20.2% to 28.2%) (Olsson et al., 1998) and lower than those reported by earlier studies in depressed older adults with schizophrenia (30% to 43%) (Cohen and Ryu, 2015; Diwan et al., 2007). These findings point to a potential gap between guidelines (Alexopoulos,

2011; Alexopoulos et al., 2001; Hasan et al., 2017; Lehman et al., 2004; Rajji et al., 2008) and the actual antidepressant prescribing practices for this population. Expert guidelines indicate that antidepressants may be useful in adjunction to antipsychotics, psychotherapeutic and psychosocial interventions among people with schizophrenia when the depressive symptoms meet syndromal criteria for major depressive episode or are sufficiently severe to cause significant distress or interfere with functioning, along with a close monitoring of psychotic symptoms, suicidality, drug-drug interactions and ECG. In addition, a recent systematic review and meta-analysis concluded that antidepressants may be effective for the treatment of depression in schizophrenia, although the evidence is mixed and conclusions are limited by the small number of low- or moderate-quality studies (Gregory et al., 2017). Further, only two studies to our knowledge (Kasckow et al., 2001; Zisook et al., 2009) have examined the efficiency of antidepressants specifically among depressed older adults with schizophrenia and have suggested their potential usefulness in this population. Taking together, our results underscore the need to disseminate guidelines more effectively for improving the diagnosis and the treatment of depression among older adults with schizophrenia (Hasan et al., 2017; Lehman et al., 2004).

Finally, we found no significant associations of SSSD with the number of antipsychotics or their type (typical or atypical). This finding is in line with previous research (Cohen et al., 1996; Zisook et al., 1999; Zisook et al., 2006) and suggests that antipsychotic monotherapy may not increase the risk of depression among older patients with schizophrenia as previous findings have suggested in younger patients (Hasan et al., 2017; Lehman et al., 2004). Although many psychosocial factors, environmental factors and general medical conditions have been implicated as risk factors for depression in clinical and community samples (Beekman et al., 1995; Hasin et al., 2005; Hoertel et al., 2015b, 2013; Kendler et al., 1995; Kessler et al., 2003; Manetti et al., 2014; Schuster et al., 2013), we found no significant associations of depression with sociodemographic characteristics, except urbanicity, and general medical conditions among older adults with schizophrenia. These results are in line with prior research that did not find significant differences in sociodemographic characteristics (Cohen and Ryu, 2015; Cohen et al., 1996; Diwan et al., 2007; Meesters et al., 2014; Zisook et al., 1999; Zisook et al., 2007) and in number of physical illnesses (Cohen and Ryu, 2015) between depressed and non-depressed older adults with schizophrenia. Taken together, these results suggest the need to regularly and systematically assess for depression among all older adults with schizophrenia spectrum disorder.

Our study has several limitations. First, depression was only measured with a self-report scale and not with a semi-structured interview. Although other rating scales such as the Calgary Depression Rating Scale (Addington et al., 1994) are validated to measure depression among individuals with schizophrenia, we chose to use the CES-D scale to favor comparability of our results with recent studies examining SSSD among older adults with schizophrenia spectrum disorder (Cohen and Ryu, 2015; Diwan et al., 2007; Meesters et al., 2014). In addition, a prior study (Doorack et al., 2007) found that the CES-D scale correlated highly ($r = 0.91$) with the Calgary Depression Rating Scale for Schizophrenia, suggesting that the CES-D scale may be as valid as this scale to screen for depressive symptoms among older adults with schizophrenia. Second, due to the cross-sectional design of this study, evidence of associations do not necessarily imply causal relationships (Le Strat and Hoertel, 2011). Third, because each participant was interviewed by only one psychiatrist and participants were recruited from a large number of centers ($n = 63$) in our study, we were unable to evaluate potential error variance in rating measurements. Fourth, the lack of a control group limits the interpretation of prevalence and risk factors of SSSD in our study. Finally, the recruiting psychiatric departments were only public-sector departments, which would possibly limit the generalizability of our findings to other types of institutions.

5. Conclusion

In a large, multicenter sample of older adults with schizophrenia spectrum disorder, we found that 78.1% of older adults had either subsyndromal (30.6%) or syndromal (47.5%) depressive symptoms (SSSD). SSSD were independently associated with positive and negative symptoms, lower quality of life, non-late-onset psychosis, benzodiazepine use and urbanicity. We found that 22.1% of patients with schizophrenia spectrum disorder and syndromal depression were treated with antidepressant medication, similar to the proportion of participants without depressive symptoms treated with antidepressants (i.e., 20.0%). Furthermore, SSSD were not associated with higher mental health care utilization, suggesting that depression may be under-assessed and/or undertreated in this population. Finally, there were no significant associations of depression with sociodemographic characteristics, except urbanicity, general medical conditions, mental health care utilization and psychotropic medications except benzodiazepines. Our findings should inform clinicians about the need to systematically and regularly assess depression in all older individuals with schizophrenia.

Acknowledgments

This study was supported by a grant from the French Ministry of Health and Social Affairs (PHRC 2008-N11-01) (<http://solidarites-sante.gouv.fr/>). It was promoted by the University of Reims Champagne-Ardenne (<http://www.univ-reims.fr/>) and the University Paris-Descartes (<https://www.univ-paris5.fr/>). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank the Clinical Research Unit of Georges Pompidou European Hospital, and in particular Pr Gilles Chatellier, Mr Yann Frigout and Mrs Pascaline Aucouturier, and the Clinical Research Unit of Robert Debré Hospital, and in particular Mrs Sarah Rubingher, Dr Bérengère Hubsch, Dr Eric Tran, Dr Fabien Gierski and Mr David Da Rin. We warmly thank all the patients and the investigators who made this study possible. Members (i.e. investigators) of the CSA Study group are: Jean Adès, Charles Alezrah, Isabelle Amado, Gilles Amar, Ovidiu Andréi, Denis Arbault, Georges Archambault, Pascaline Aucouturier, Gilles Aurifeuille, Hervé Bardou, Michèle Bareil-Guérin, Pierre Barrau, Claudine Barrouillet, Emilie Baup, Nadine Bazin, Béatrice Beauvils, Jalel Ben Ayed, Michel Benoit, Kader Benyacoub, Thérèse Bichet, Françoise Blanadet, Olivier Blanc, Julien Blanc-Comiti, Didier Boussiron, Anne-Marie Bouysse, Alain

Brochard, Olivier Brochart, Bastien Bucheron, Marion Cabot, Vincent Camus, Jean-Marc Chabannes, Véronique Charlot, Thomas Charpeaud, Gilles Chatellier, Cateline Clad-Mor, Colette Combes, Maricela Comisu, Sylvain Cordier, François Costi, Jean-Paul Courcelles, Mercedes Creixell, Henry Cuche, Anis Dammak, David Da Rin, Jean-Bernard Denis, Hélène Denizot, Anne Deperthuis, Eric Diers, Smail Dirami, Didier Donneau, Pierre Dreano, Caroline Dubertret, Eric Duprat, Didier Duthoit, Christian Fernandez, Philippe Fonfrede, Nelly Freitas, Yann Frigout, Philippe Gasnier, Jacques Gauillard, Fabien Getten, Fabien Gierski, Fabien Godart, Raphaël Gourevitch, Aude Grassin Delye, Juliette Gremion, Hélène Gres, Véronique Griner, Christian Guggiari, Olivier Guillin, Hamadi Hadaoui, Emmanuel Haffen, Cécile Hanon, Sadeq Haouzir, Cyril Hazif-Thomas, Anne Heron, Bérengère Hubsch, Isabelle Jalenques, Dominique Januel, Jean-François Karnycheff, Oussama Kebir, Marie-Odile Krebs, Christine Lajugie, Marion Leboyer, Pierre Legrand, Michel Lejoyeux, Vincent Lemaire, Evelyne Leroy, Diane Levy-Chavagnat, Antoine Leydier, Chantal Liling, Pierre-Michel Llorca, Philippe Loeffel, Patrice Louville, Stéphane Lucas Navarro, Nicolas Mages, Mohamed Mahi, Odile Maillet, Aude Manetti, Catherine Martelli, Pascal Martin, Marc Masson, Isabelle Maurs-Ferrer, Joelle Mauvieux, Sylvain Mazmanian, Emmanuelle Mechin, Lila Mekaoui, Mostéfa Meniai, Agnès Metton, Amine Mihoubi, Maria Miron, Geneviève Mora, Valérie Niro Adès, Philippe Nubukpo, Cécile Omnes, Stéphanie Papin, Pierre Paris, Christine Passerieux, Jérôme Pellerin, Sylvie Perron, Annie Petit, François Petitjean, Dominique Pringuey, Andrei Radtchenko, Hassan Rahiou, Anne Rauzy, Lionel Reinheimer, Michel Renard, Margaux René, Charles-Edouard Rengade, Paul Reynaud, Didier Robin, Christelle Rodrigues, Aurélie Rollet, Fabien Rondepierre, Bernard Rousselot, Sarah Rubingher, Ghassen Saba, Jean-Pierre Salvarelli, Jean-Claude Samuelian, Corinne Scemama-Ammar, Franck Schurhoff, Jean-Pierre Schuster, Daniel Sechter, Béatrice Segalas, Tiphaine Seguret, Anne-Sophie Seigneurie, Amina Semmak, Frédéric Slama, Sophie Taisne, Mohamed Taleb, Jean-Louis Terra, Dominique Thefenne, Eric Tran, Rémi Tourtauchaux, Marie-Noëlle Vacheron, Pierre Vandel, Valérie Vanhoucke, Emmanuel Venet, Hélène Verdoux, Anne Viala, Gilles Vidon, Murielle Vitre, Jean-Luc Vurpas, Carole Wagermez, Michel Walter, Liova Yon, Xavier Zendjidjian.

Author contributions statement

NH and FL designed the study. FL obtained the funding. FL, SB, YB, DRC, CBP, CCL supervised patient recruitment. CP, AC and NH undertook data management. NH and RPDR undertook statistical analyses. NH and CJ wrote the first draft of the manuscript. RPDR, KM, SB, YB, CP, DRC, CBP, CCL, AC, CGL, CL, GA, HP, AK and FL critically reviewed the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

FL has received speaker and consulting fees from AstraZeneca, Janssen, Lundbeck, Otsuka Pharmaceuticals, Roche and Servier outside the submitted work. DRC reports personal fees from Lundbeck and Otsuka, unrelated to the submitted work. CBP reports personal fees from Lundbeck, Otsuka and Janssen, unrelated to the submitted work. CL reports personal fees and non-financial support from Lundbeck, personal fees from Janssen, non-financial support from Otsuka Pharmaceuticals, outside the submitted work. AK reports personal fees from Euthérapie, Lundbeck, Otsuka and Janssen, unrelated to the submitted work. Other authors report no conflicts of interest relevant to the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jad.2019.03.007](https://doi.org/10.1016/j.jad.2019.03.007).

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