Sexual dysfunctions are associated with major depression, chronic inflammation and anticholinergic consumption in the real-world schizophrenia FACE-SZ national cohort. Running title: sexual dysfunctions in schizophrenia

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Abstract

Background. Sexual dysfunctions (SD) are frequent in schizophrenia (SZ) and associated with treatment withdrawal, however they remain under-explored and under-treated. To date, most of the studies have focused on SD as antipsychotics' side effects in therapeutic trials.

Aims. The objectives of the present study were to determine the SD prevalence in stabilized SZ outpatients and their clinical, pharmacological and biological correlates.

Method. 237 participants (61.2% men) were consecutively included and received a thorough 2 days- clinical assessment including the self-reported Sexual Functioning Questionnaire (SFQ). SD was defined by a SFQ score ≥8.

Results. 237 subjects were recruited in the FACE-SZ cohort, 41% of them reported sexual dysfunctions. In multivariate analyses, SD have been associated with current major depressive disorder (adjusted odd ratio aOR=2.29[1.08-4.85],p=0.03), anticholinergic prescription (aOR=2.65, p=0.02) and chronic low-grade inflammation (aOR=2.09,p=0.03) independently of age, gender, current cannabis use disorder and olanzapine prescription. No antipsychotic has been associated with increased or decreased SD rate.

Conclusions. SD are frequent in SZ subjects. Major depression, anticholinergic prescription and chronic low-grade peripheral inflammation may be the three targets of interest for addressing this specific issue.

Declaration of interest. None.

Keywords: sexual dysfunctions; schizophrenia; antipsychotics; major depression; inflammation

Introduction

Sexual dysfunctions (SD) are defined by the inability of a person to have one or all stages of sexual activity including desire, excitement, erection/ejaculation for men, vaginal lubrification for women and orgasm. SD are frequently reported by patients treated by psychotropic drugs, however they have remained underestimated and undertreated for decades.

Subjects with schizophrenia (SZ) have a specific increased risk of SD compared to other psychiatric patients due to antipsychotic consumption that may induce hyperprolactinemia. The current international recommendations in case of antipsychotic-induced SD are (i) antipsychotic dose decrease, (ii) change to a prolactin-sparing antipsychotic, (iii) adding aripiprazole and (iv) phosphodiesterase inhibitors (Stroup and Gray, 2018). The authors of these recommendations stipulated that the evidence for specific symptom treatments (other than phosphodiesterase inhibitors for erectile dysfunction) was lacking (Stroup and Gray, 2018).

However, SD may not always be due to antipsychotic drug consumption. SZ patients are exposed to other SD risk factors that have been identified in non-SZ populations, including other psychotropic drugs consumption (especially antidepressants, benzodiazepine and anticholinergics), being single, major depression, metabolic syndrome, tobacco smoking and chronic peripheral inflammation (G. Fond et al., 2018; Godin et al., 2015, 2018; Martín et al., 2018). In summary, there is a lack of knowledge on SD in real-world SZ outpatients and on which factors may be associated to increased SD.

The objectives of the present study were to determine the prevalence of sexual dysfunctions in the stabilized real-world SZ outpatients of the FACE-SZ national cohort and their clinical, pharmacological and biological correlates.

Population and methods

The FACE-SZ cohort has been extensively described in previous studies (Schürhoff et al., 2018, 2015). **The details of the FACE-SZ cohort (study**

population, diagnosis process, collected data, ethical concerns) are provided in supplementary material (Annex 1).

SD definition

Subjects completed the Sexual Functioning Questionnaire (SFQ), a self report structured instrument that has been previously validated in patients with psychotic disorders (Smith et al., 2002). The SFQ includes subscales assessing libido, physical arousal, erectile function, orgasm and ejaculatory function. Some items are reversed. The score is +1 if the patient has answered "yes" to an item (presence of sexual dysfunction), or "no" to a reversed item (absence of normal sexual function). Higher scores indicate greater impairment, and a total SFQ score ≥ 8 is the cut-off indicating sexual dysfunction.

Sociodemographic, clinical, pharmacological and biological variables

The clinical scales and metabolic data has been previously comprehensively described (Schürhoff et al., 2015) and are available in supplementary material. As the clinical evaluation and the biological analyses were separated in time and location, the clinical evaluation and the biological analyses were both blinded. Depressive symptoms were evaluated using the Calgary Depression Rating Scale for Schizophrenia (CDRS (Addington et al., 1992; Lançon et al., 2000)). Chronic low-grade peripheral inflammation was defined by a high sensitivity C-reactive protein (hs-CRP) ≥3 mg/L (Fond et al., 2016) and was measured with an assay using nephelometry (Dade Behring) blinded to schizophrenia status.

Statistical analysis

Socio-demographics, clinical characteristics, addictive behaviour, treatments, biological 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 between respectively SD and non-SD subjects regarding demographic, clinical, pharmacological and biological variables were performed

using the chi-square test for categorical variables. Continuous variables were 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 analyses were included in the multivariate analyses (table 2 (whole sample): current cannabis use disorder, major depressive disorder, anticholinergics, olanzapine, peripheral inflammation, table 3 (men): age, education level, current cannabis use disorder, major depressive disorder, first generation antipsychotics, quetiapine, chronic peripheral inflammation; table 4 (women): age, education level, major depressive disorder, anticholinergics, chronic peripheral inflammation). Age and gender were forced in the first model (whole sample) (table 2). 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 (Bender and Lange, 2001). Analyses were conducted using SPSS 17.0 software (SPSS Inc., Chicago, IL). All statistical tests were two-tailed, with α level set at 0.05.

Results

237 subjects (145 men and 92 women) were included in the present study. Overall, 96 (40.5%) reported SD (63 (43.4% men and 33 (34.4%) women with no difference between genders (p=0.25)). 13 subjects were diagnosed with sleep apnea, none of them reported SD. None of the participants reported history of cardiovascular or neurological events (including myocardial infarction, stroke or meningitis), sexually transmitted chronic viral infection (including B and C hepatitis or HIV), addiction to heroin or to opioids or took substitute treatment or phosphodiesterase inhibitors.

The frequency of responses for each SFQ item is described in table 1. Only 42.6% of the participants reported a sexual activity during the last month. 19.8% reported a total absence of sexual desire, 29.1% difficulties in reaching sexual arousal and 13.1% an absence of orgasm during the last month. 42.2% reported reaching sexual arousal without physical reaction. Almost 10% of the men reported a total absence of erection during the last month.

The factors associated with SD are presented in table 2 (whole sample), 3 (men) and 4 (women). In multivariate analyses, SD have been associated with current major depressive disorder (adjusted odd ratio aOR=2.29[1.08-4.85], p=0.03), anticholinergic prescription (aOR=2.65[1.14-6.14], p=0.02) and chronic low-grade inflammation (aOR=2.09[1.08-4.06],p=0.03) independently of age, gender, current cannabis use disorder and olanzapine prescription. No other psychotropic drug (especially antipsychotics and antidepressants) has been associated with increased or decreased SD rate. No dose-effect has been found for any antipsychotic (data not shown, all p>0.05). In men, SD were associated with older age (aOR=1.07[1.01-1.14], p=0.02), lower education level (aOR=0.74[0.61-0.89], p<0.001), major depressive disorder (aOR=2.99[1.06-8.49], p=0.04) independently of first-generation antipsychotic prescription, quetiapine prescription and peripheral inflammation. In women, SD were associated with younger age (aOR=0.93[0.87-0.99],p=0.04) and anticholinergic prescription (aOR=5.87[1.09-31.47],p=0.04) independently of education level, major depressive disorder and peripheral inflammation.

Major depressive disorder was more specifically associated with increased arousal difficulties (63.0 vs. 30.1%, p=0.001), incomplete erections (28.3 vs.12.8%, p=0.02), important delay between orgasm and ejaculation (57.7 vs. 33.6%, p=0.02), and orgasm difficulties (61.5 vs. 38.1% vs. p=0.03). Peripheral inflammation was associated with increased absence of erection and absence of full erection in men (27.8 vs. 13.0% vs. p=0.04 (item 12) and 40.5 vs. 20.6% (item 15)), with rare erections (43.2 vs. 20.6%, p=0.08) (item 16)), with difficulties in reaching full erection when desired (62.2 vs. 34.7%, p=0.004), with absence of orgasm in men and women (24.3 vs. 9.0%, p=0.02). Anticholinergic prescription was associated with absence of sexual thought (28.6 vs. 12.4%, p=0.02) and decreased sexual attraction (35.7 vs. 11.9%, p=0.002).

Discussion

The present findings may be summarized as follows: in a non-selected sample of SZ outpatients, almost 41% reported SD that were independently associated with major depressive disorder (but not antidepressant consumption), chronic low-grade peripheral inflammation and anticholinergic consumption. Anticholinergic was specifically associated with SD in women, while major depression was specifically

associated with SD in men. Age was found to have a small but contrary effect in men and women. Major depression was found to be associated with arousal, erection, ejaculation and orgasm issues, while peripheral inflammation was associated with erection and orgasm issues and anticholinergics with sexual desire issues.

The first result of the present study is that 41% of stabilized SZ outpatients report SD, which is high compared to the general population but lower compared to previous studies exploring SD in SZ out or inpatients (beyond 50%) (Fan et al., 2007; Howes et al., 2007). The observational studies using the SFQ questionnaire are scarce, this questionnaire having been mostly used in controlled trials to measure the antipsychotics sexual side effects. This prevalence is also similar to those found in older non-SZ populations. This is consistent with previous FACE-SZ analyses suggesting accelerated aging processes in SZ subjects (and more specifically aging related to chronic peripheral inflammation, the so-called "inflammaging") (Bulzacka et al., 2016). Comparing this rate to other SZ populations is difficult given the high number of confounding factors (including country, age, sex ratio, age at illness onset, tool to evaluate SD, treatments, comorbidities, lifestyle). However this high prevalence is an alarm call for clinicians to systematically assess SD in SZ outpatients. Beyond current recommendations for SD management summarized in the rationale of the present study, our findings may yield other strategies for SD management in SZ outpatients.

Altogether, these results suggest that SD may not be only an antipsychotic drug-induced issue in SZ outpatients. The absence of association between the classes of antipsychotics (first vs. second generation) confirms previous findings suggesting adverse effect profiles being specific to each antipsychotic medication and doing not neatly fit into first- and second-generation classifications (Stroup and Gray, 2018). It should be underlined that no specific antipsychotic has been associated with increased or decreased SD in the present sample, especially aripiprazole that is currently recommended in case of SD onset (Stroup and Gray, 2018). Long-acting antipsychotics administration was also not associated with decreased SD, while it may have been suggested that more stable antipsychotic blood dosage may have decreased their side effects.

On the contrary, SD have been associated with chronic peripheral inflammation (but not metabolic syndrome that may be a confounding factor). This is consistent with previous findings in non-SZ populations with chronic metabolic

diseases (Maiorino et al., 2018). More specifically, endothelial inflammation may induce a decreased nitric-oxide-mediated relaxation (Santi et al., 2016) that may explain the association between peripheral inflammation and decreased erection reported in the SZ men in our study. All sex steroid hormones (specifically DHEA, DHEAS and testosterone) have shown anti-inflammatory properties and have been shown to improve physical well-being, muscle strength and bone density, and reduces body fat (Prall and Muehlenbein, 2018; Rutkowski et al., 2014). A bidirectional relationship between chronic peripheral inflammation and SD could therefore be hypothesized. DHEA has also been shown to improve psychological well-being, which may be particularly useful in SZ patients with both SD and major depression. Beyond SD, sex steroid hormones have shown multiple potential benefit in SZ subjects (for review see (Soria et al., 2018)). Anti-inflammatory strategies have shown effectiveness on SZ and depressive symptomatology (Fond et al., 2014), future studies should confirm if they may also improve sexual health of SZ patients.

SD have been associated with major depression in the present study, but not with psychotic symptomatology (and especially not with negative symptoms some of which being common with depression like anhedonia or avolition). While this mutual association of SD and depression was well known in mood disorders and general population (Porto, 2014), it has been found for the first time in schizophrenia. Major depression has been previously associated with impaired quality of life in schizophrenia independently of negative symptoms (Andrianarisoa et al., 2017) and remains underdiagnosed and undertreated (Guillaume Fond et al., 2018). The absence of association of antidepressants administration with SD may be explained by the coprescription of antipsychotics that may erase this association, all patients being treated in the present study. The present results therefore suggest that SZ subjects with SD should be evaluated for depression and treated if needed, as antidepressants have shown effectiveness in major depression in SZ patients (Guillaume Fond et al., 2018). The present results suggest that this association was found in men but not in women. This result should be taken with caution, as only 21 SZ women with major depression were included in the study, which may have led to power lack.

Anticholinergics have been associated with SD, and specifically with decreased sexual desire in SZ women in the present study. The sexual side-effects of drugs interfering with cholinergic transmission are known for decades (Aldridge, 1982). Our results are consistent with those of a previous recent study (Rubio-Abadal

et al., 2016). SZ women receiving anticholinergics have reported more than 4 times higher SD rates in our study, however only 10 SZ women were administered anticholinergics, which highlight the need to replicate this finding in a larger sample. It seems reasonable to suggest a background regimen modification or an antipsychotic dose decrease with anticholinergic drug withdrawal in case of SD, as anticholinergic have other side effects including cognitive impairment.

While more than 50% of SZ subjects are smokers, no association between tobacco smoking and SD has been found in the present sample, which is not consistent with previous results (Liu-Seifert et al., 2009; Uçok et al., 2007). This may be explained by the young middle age of our sample (32 years) while tobacco smoking has been associated with SD mostly in populations mean aged >40 years (Biebel et al., 2016). However, it seems still reasonable to recommend tobacco smoking cessation to all SZ smokers to avoid later SD onset in addition to other health outcomes. More than 85% of the SZ patients were single in our study, but this has not been found to be associated with increased SD risk contrary to previous findings in non-SZ population. The hypothesis of a bilateral relationship between SD and singleness in SZ patients is therefore not validated in our sample. SZ patients have been more exposed to childhood trauma compared to the general population, but this has not been found as a risk factor for SD in adulthood in our population. Education level and age at illness onset, duration of untreated psychosis were also not associated with increased SD rates. The increase of SD prevalence with age in men has been classically described in both SZ and non-SZ population(Liu-Seifert et al., 2009), which suggests that our sample may be representative of real-world stabilized SZ outpatients.

Strengths. The multicentric recruitment, the inclusion of never-previously explored dimensions in the field of SD (including history of childhood trauma, duration of untreated psychosis, age at first thymic episode, chronic peripheral inflammation with highly sensitive CRP dosage, hypovitaminosis D, metabolic syndrome), the use of a validated self-reported questionnaire to explore SD (and not simply asking during a semi-structured interview) and the multivariate analysis including confounding factors may be highlighted in the strengths of the present study. The metabolic syndrome parameters were measured during evaluation and not only reported by questionnaires or interviews. While the sample size may appear as limited, the present study is one of the largest study exploring SD in SZ outpatients.

The limited number of included patients was due to ethical restriction, the French Ethical Committee having classified SD data as sensible research data. The SFQ questionnaire was therefore not disseminated to all patients but only in the patients participating in the Psy-Coh project follow-up study (Schürhoff et al., 2018). Choosing between hetero-reported and self-reported questionnaires is an old an unresolved debate (Misdrahi et al., 2016). Each choice has its own advantages and disadvantages. In the present study, it was hypothesized that self-questionnaire would improve the acceptability to respond to intimate questions. However, almost 20 self-reported and hetero-rated questionnaires have been developed to explore SD and there is no gold standard to date. A systematic review should be carried out as well as qualitative studies to determine which tools may be the more appropriate to explore SD in SZ subjects.

Limits. Race/ethnicity has not been reported due to ethical issues. A healthy lifestyle based on dietary pattern with high content of whole grain, fruit, nuts and seeds, and vegetables and low in sodium and saturated fatty acids plus regular physical activity may help to modulate the pro-inflammatory state associated with the related burden of sexual dysfunctions (Khoo et al., 2011). Lifestyle (including sleep disorders, diet and physical activity) should therefore be included in future studies exploring SD in SZ subjects. The number of patient treated by amisulpride (N=11) was insufficient to comprehensively explore the potential associations of amisulpride with SD. Sexual hormones and prolactinemia dosages have not been carried out as it is not recommended in clinical routine practice according to recent recommendations (Stroup and Gray, 2018). Like most of the previous studies, all patients were treated in the present study; it is therefore difficult to unravel specific factors due to schizophrenia itself. Antidepressants were analyzed as a class and subclasses, however each antidepressant may have a specific side-effect profile, future studies should compare more specifically each antidepressants to determine those at lower risk of SD onset in SZ subjects.

Perspectives. Sildenafil remains an effective option for men with persistent erectile dysfunction if the above-mentioned interventions have not been effective (Kaminetsky et al., 2017). Exploring the impact of SD (and their improvement) on quality of life in SZ real-world outpatients is also a major issue for future studies.

Conclusion

Future recommendations for the care of SZ subjects should systematically include sexual dysfunctions. This exploration should not be limited to antipsychotic drug background regimen modifications. The present findings suggest that treating major depression, withdrawing anticholinergics (with decreasing the dose or switching the antipsychotic after benefit/risk evaluation, especially in case of decreased sexual desire), and improving chronic peripheral inflammation (by complementary agents or lifestyle habits modifications), especially in case of erection or orgasm issues, may be the three major interventions to address sexual dysfunctions in SZ subjects. Sex steroid hormones should also be further explored in case of non-response to these three strategies.

For sections “conflicts of interest” “acknowledgments” and “contributors” see supplementary material Annex 1.

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