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Sexual dysfunctions in schizophrenia: beyond antipsychotics. A systematic review.

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Abstract

Background. Sexual dysfunctions (SD) in schizophrenia are frequent with strong impact on adherence and quality of life. Current recommendations stipulate to switch to prolactin-sparing antipsychotic in case of SD.

Objectives. To synthesize in a systematic review data on the SD prevalence and the associated risk factors in schizophrenia (SZ).

Methods. Medline, Google Scholar, PsychInfo, and Cochrane were explored, without any year or language restriction.

Results. Overall, 89 studies and 25,490 participants were included in the present review. SZ subjects aged 18-70 reported high SD frequency [30%-82%] (men [33%- 85%]; women [25%-85%]). For SZ men erectile dysfunction [31%-95%] was the most frequent SD vs. loss of libido for women [31%-100%]. The following risk factors were associated with increased SD: 1. Illness severity (including psychotic symptomatology, early age at SZ onset, negative symptomatology, and continuous illness course), 2. Depressive symptomatology 3. Antipsychotics (especially first generation antipsychotics, risperidone and antipsychotic polytherapy). Switching to prolactin-sparing antipsychotics has shown effectiveness in some studies (especially aripiprazole). Antidepressants were not found to be associated with SD in SZ subjects.

Conclusion. The prevalence of SD is high in SZ subjects. In addition to the current guidelines, the present review suggests that treating depressive symptoms may be a major intervention to improve SD in SZ subjects. Sociodemographic variables, physical illnesses, metabolic syndrome and peripheral inflammation have been poorly or never explored and should be included in future studies.

Declaration of interest: None

Keywords: sexual dysfunctions, schizophrenia, psychotropic drugs, addiction, prolactin, depression

1. INTRODUCTION

Sexual dysfunctions (SD) are defined by the inability to reach one or all stages of sexual activity including desire, excitement, vaginal lubrication for women, erection/ejaculation for men and orgasm (Langis et al., 2015). SD are reported by 40 to 50% of women (Laumann et al., 1999; Lewis et al., 2010; McCabe et al., 2016; Rosen et al., 2000) and 30% to 50% of men in the general population (DeRogatis and Burnett, 2008; Laumann et al., 1999; Lewis et al., 2010; McCabe et al., 2016; Rosen et al., 2000), mostly after 40 years. SD are increased in psychiatric populations due to psychiatric symptomatology and psychotropic drugs; however, they remain underexplored and undertreated (Serretti and Chiesa, 2011; Uçok et al., 2008). A recent review exploring the side effects of antipsychotic drugs has concluded that SD were insufficiently explored and should be integrated in the therapeutic strategy (Stroup and Gray, 2018)

The risk of SD onset is particularly high in schizophrenia (SZ), due to antipsychotic medication but also intrinsic illness factors including age at illness onset, psychotic severity, negative and depressive symptoms (Fond et al., 2018), addictions (Mallet et al., 2017), impaired lifestyle habits (decreased physical activity, sleep disorders and unhealthy diet), chronic somatic illnesses (diabetes, hypertension, overweight) (Godin et al., 2015) and peripheral inflammation. SD have been identified as one of the most frequent reported motive for treatment discontinuation in SZ and have been associated with impaired quality of life in SZ subjects (A. Heald, 2010; Bebbington et al., 2009; Lambert et al., 2004). SD may therefore directly impact the illness course and the risk of relapse (Baldwin, 2001; Perkins, 2002; Serretti and Chiesa, 2011). However most of the available data comes from randomized controlled trials with highly selected patients and little is known about other pharmacological treatments and confounding factors in real world schizophrenia, including comorbidities, addictions and polytherapy. For example, in real-world SZ care, one third of the subjects are administered antidepressants (Fond et al., 2018). It has been estimated in a cross-sectional study of 502 non-SZ adults with major depressive disorders, that one third of the patients treated with antidepressants have reported a drug-induced SD (Williams et al., 2006) but it remains unclear if depression or antidepressant may increase the risk of SD onset and/or maintenance in SZ.

The objectives of the present study were to synthesize in a systematic review the data on the prevalence and risk factors of SD in schizophrenia.

2. METHODS

This review is based on the PRISMA (Preferred Reporting items for Systematic reviews and Meta-analysis) and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) criteria. The systematic bibliographic searches have been carried out according to the Cochrane methodology exploring the following databases: Medline, Google Scholar, PsychInfo, and Cochrane. Each database has been searched from inception to September 2018. The associated articles and the list of references of the included studies were also explored. The primary paradigm was developed with the MESH for Medline: “schizophrenia AND sexual dysfunctions” and replicated or adapted for each base. A second search based on the identified scales for SD assessment was carried out (see below for the list of the scales).

Inclusion criteria: all observational studies exploring SD in stabilized outpatients with a CIM or DSM diagnosis of SZ.

Non-inclusion criteria: The studies including patients other axis I diagnoses except for major depressive disorders, eating disorders and anxiety disorders were not included, as well as animal studies.

Two independent reviewers (MD and GF) decided on the eligibility of each study and extracted the data in a standardized electronic form. In case of non-consensus, a third author (LB) made the final decision. When it was possible, the authors were contacted by email in case of missing data. Four teams were contacted (Byerly et al., 2006; Konarzewska et al., 2009; Mahmoud et al., 2012a, 2011a; Ong et al., 2014a). but none of them answered.

Overall, 20 scales to assess SD in SZ subjects were identified (12 validated and 8 non-validated or created specifically for the study) and presented in the **Table 1**:

-Validated hetero-questionnaires: Sexual items from the Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU SERS)(Bobes et al., 2003; Hummer et al., 1999) (N= 12); the Changes in Sexual Functioning Questionnaire (CSFQ) (Clayton, 1997) (N= 10); the Sexual Functioning Questionnaire (SFQ) (Burke et al., 1994; Smith et al., 2002) (N= 7); the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) (Montejo et al., 2000) (N= 4); the Antipsychotics and Sexual Functioning Questionnaire (ASFQ) (McGahuey et al., 2000) (N= 3) .

-Validated self-reported questionnaires: the Arizona Sexual Experience Scale (ASEX) (McGahuey et al., 2000) (N= 17); the Derogatis Interview for Sexual functioning (DISF) (Derogatis, 1997) (N= 3); the Dickson Glazer Sexual Functioning Scale (**DGSF**) (Dickson, R.A., Glazer, W.M., and Violato, C, 2001) - (N= 3); the international index of erectile function (IIEF) (Rosen et al., 1997) (N= 2); the Nagoya Sexual Function Questionnaire (NSFQ) (Kikuchi T, 2011) (N= 2); the Female Sexual Functioning Index (FSFI) (Rosen et al., 2000) (N= 1); the Antipsychotic non neurological side effects rating scale (ANNSERS) (Mahmoud et al., 2011b) (N= 1); Multidimensional Sexuality questionnaire

(Snell, Fisher, et Walters 1993) (N= 1).

Except for the DGFS, all scales were not specific of SZ subjects. The ANNSERS and the PRSexDQ were developed specifically to assess antipsychotic-induced SD.

3. RESULTS

The search of Medline, Google Scholar, PsychInfo, and Cochrane provided a total of 40,216 references. The selection process is presented in **Figure 1**. The references of the articles were checked to detect additional references. No studies were obtained from the grey literature. A total of 89 studies and 25,490 participants were included in the final qualitative synthesis.

Disagreements were resolved by consensus among all authors. The design of the studies, data extraction and data synthesis are described in **Table 1**.

3.1 Prevalence and type of SD

SZ men and women treated by antipsychotics reported high rates of SD [30-82%], [33%-85%] for SZ men vs. [25%-85%] for SZ women (Alves Nunes, 2009; Bobes et al., 2003; Bram et al., 2014; Dossenbach et al., 2005; Fanta et al., 2018, 2018; Ghadirian et al., 1982; Harley et al., 2010; Hou et al., 2016; Kelly and Conley, 2003; Martín et al., 2018; Millier et al., 2014; Montejo et al., 2010; Nakhli et al., 2014; Olfson et al., 2005; Rubio-Abadal et al., 2016; Simiyon et al., 2016; Ucok et al., 2007).

3.2 Sociodemographics

Gender (cross sectional studies N= 24, 13,861 SZ subjects and case-control studies N= 13; 1595 SZ subjects vs. 1240 controls) (Aizenberg et al., 1995; Alves Nunes, 2009; Bobes et al., 2003; Dembler-Stamm et al., 2018; Fanta et al., 2018; Fortier et al., 2003; Fujii et al., 2010; Harley et al., 2010; Hocaoglu et al., 2014; Hou et al., 2016; Howes, 2007; Kockott and Pfeiffer, 1996; Kokoszka and Kwiatkowska, 2010; Macdonald et al., 2003; Ong et al., 2014a; Simiyon et al., 2016; Smith et al., 2002; Ucok et al., 2007)

In decreased order of frequency, SZ men reported mostly erectile dysfunction followed by loss of libido while SZ women reported mostly loss of libido followed by excitement dysfunction. More specifically, the specific SD were (in order of decreasing frequency): loss of libido (both gender [28%-54%]; SZ M[26%-94%]; SZ W[31%-100%]), excitement dysfunction (both gender [38%-57%]; SZ M[26%-87%]; SZ W[17%-93%]), erectile dysfunction (SZ M[31%-95%]), ejaculation dysfunction (SZ M[64%]), premature ejaculation (SZ M[32%-49%]), delayed

ejaculation (M[64%]), vaginal lubrication dysfunction (SZ W[31%-66%]), vaginal pain (SZ W[32%-37%]), orgasmic dysfunction (SZ M[24%-94%]; SZ W[23%-78%]).

Overall, case-control studies confirmed the same data than cross-sectional studies with lower sample sizes. Compared to controls, SZ men had less sexual desire [17%-52%] vs. [5%-12%], had more excitement dysfunction [35%-48%] vs. [4%-31%], were less likely to achieve erection [21%-54%] vs. [8%-20%], had more premature ejaculation [25%-35%] vs. [3%-20%], had more reduced ejaculatory volume/anejaculation [26%] vs. [4%], and reported more orgasmic dysfunction [26%-48%] vs. [8%-15%].

SZ women had less sexual desire ([19%-73%] compared to controls [12%-68%]), more excitement dysfunction ([40%-71%] vs. [6%-58%]), more genital pain ([8%-20%] vs. [3%-8%]), more vaginal lubrication dysfunction ([30%-63%] vs. [6%-49%]) vaginismus (SZ W[44%]) and more orgasmic dysfunction ([11%-58%] vs [11%-44%]).

Age (N= 7; 1,628 SZ subjects)

SZ men were found to report more SD compared to their controls of the same age (Fujii et al., 2010). More specifically, from 18 to 50s they reported more erectile dysfunction, loss of libido, ejaculation and orgasm dysfunctions than their controls; over 50, they reported more ejaculation dysfunction (as the other SD increase in the control groups after 50) (Fujii et al., 2010). The SZ women mean aged 30s reported higher loss of libido than their controls (Fujii et al., 2010).

SD was found to increase with age both in SZ and control groups (especially for decreased libido and excitement dysfunction erectile and ejaculatory dysfunctions for SZ men), with an earlier onset in SZ (Hou et al., 2016; Mahmoud et al., 2012a; Malik et al., 2011; Smith et al., 2002). These SD were increased by 40% with each 10-year age increase in SZ men (Konarzewska et al., 2009).

Relationship status (N= 5; 1318 SZ subjects)

Being single (Fanta et al., 2018; Hou et al., 2016; Martín et al., 2018), divorced (Fanta et al., 2018; Martín et al., 2018), unmarried (Lee et al., 2015) and have been associated with increased SD in SZ subjects as well as poor marital quality of life for SZ women (Simiyon et al., 2016).

Educational, socio-professional and economical level (N= 1; 827 SZ subjects)

Unemployed SZ subjects and those with lower income were found to have increased rates of SD compared to those with occupation and upper income (Ucok et al., 2007).

3.3 Psychotic symptomatology (N= 21; 4230 SZ subjects)

SD have been associated with current psychotic symptomatology independently of the antipsychotic medication status, in both genders (Aizenberg et al., 1995; Bo et al., 2016; Bram et al., 2014; Fan et al., 2007; Fortier et al., 2003; Kelly and Conley, 2003; Kockott and Pfeiffer, 1996; Lee et al., 2015; Lyketsos et al., 1983; Macdonald et al., 2003; Malik et al., 2011; Millier et al., 2014; Olfson et al., 2005; Ong et al., 2014a; Simiyon et al., 2016; Ucok et al., 2007; Westheide et al., 2008).

Increased SD are reported from the first psychotic episode (Bram et al., 2014; Pfeiffer et al., 1991). Increased loss of sexual desire has been associated with negative symptoms in both genders. The risk of SD was increased in patients with earlier age at illness onset, higher lifetime number of psychotic episodes (Fanta et al., 2018), higher number of lifetime hospitalizations (Acuña et al., 2010; Lyketsos et al., 1983), and continuous illness course (Nakhli et al., 2014; Ong et al., 2014b).

Positive symptoms have been associated with lower orgasm dysfunction (Ong et al., 2014a) and increased libido in SZ men (Malik et al., 2011) and with loss of sexual desire (Ong et al., 2014a), excitement (Fan et al., 2007; Ong et al., 2014a), and orgasm dysfunctions (Fan et al., 2007) in SZ women.

3.4 Major depression and antidepressants (N= 4; 283 SZ subjects)

Major depression has been associated with increased SD in SZ subjects (Fan et al., 2007; Martín et al., 2018; Smith et al., 2002). For antidepressants, only one interventional study has found that mirtazapine may improve orgasmic dysfunction in both gender, all patients being administered FGA in this study (Terevnikov et al., 2017).

3.5 Addictive Comorbidity (N= 3; 1056 SZ subjects)

Inconsistent results have been found in regard of the relationship of tobacco smoking and SD, two studies reporting non significant results and one reporting higher sexual desire in male SZ tobacco smokers (Lee et al., 2015; Macdonald et al., 2003; Ucok et al., 2007) . The impact of alcohol, cannabis and other drug consumption has not been explored in SZ subjects.

3.6 Antipsychotic drugs

First Generation Antipsychotics (FGA) (N= 18; 20,433 SZ subjects)

Without treatment distinction, FGA has been associated with more frequent and more pronounced SD than second-generation in both SZ men and women (Bitter et al., 2005; Costa et al., 2007;

Hou et al., 2016; Kelly and Conley, 2006; Liu-Seifert et al., 2009; Mahmoud et al., 2011a; Montejo et al., 2010; Ucok et al., 2007; Wirshing et al., 2002). Thioridazine was significantly associated with higher level of SD compared to other FGA, particularly for erection and ejaculatory dysfunction (Kotin et al., 1976).

Haloperidol was associated with more SD compared to risperidone at the dose of 2mg/d but not in higher daily doses (Bobes et al., 2003; Dossenbach et al., 2006; Peuskens, 1995). Beyond 12 mg/d, the risk of SD onset was superior for risperidone compared to haloperidol 10 mg/d (Peuskens, 1995). Long-acting FGA were associated with a similar risk of SD than oral FGA (Mahmoud et al., 2011a; Montejo et al., 2010). Increased daily doses of FGA were particularly associated with erectile dysfunction for SZ men and excitement dysfunction for SZ women (Smith et al., 2002).

FGA-induced SD was associated with increased prolactin (PRL) blood levels (Ahl et al., 2004; Burke et al., 1994; Ghadirian et al., 1982) which has been associated with increased erectile and orgasm dysfunction for SZ men (Smith et al., 2002) and loss of libido (Dossenbach et al., 2005; Smith et al., 2002) and vaginal lubrication dysfunction in SZ women (Smith et al., 2002).

Second Generation Antipsychotics (SGA)

Risperidone (N= 26; 12,719 SZ subjects), Amisulpride (N= 1; 244 SZ subjects), Olanzapine (N= 10; 8911 SZ subjects), Clozapine (N= 7; 1381 SZ subjects), Quetiapine (N= 12; 10379 SZ subjects), Aripiprazole (N= 12; 1357 SZ subjects)

The second-generation antipsychotics have been classified in the following order of decreased risk of SD onset with various levels of evidence: Risperidone> amisulpride> olanzapine> clozapine> quetiapine> aripiprazole (Ahl et al., 2004; Bitter et al., 2005; Ciudad et al., 2007; Dossenbach et al., 2006, 2005; Fortier et al., 2003; Kim et al., 2002; Knegtering et al., 2006, 2004; Nakonezny et al., 2007; Sathish Kumar and Sinha, 2015; Spollen et al., 2004; Tran et al., 1997; Ucok et al., 2007; Wang et al., 2016; Yasui-Furukori et al., 2012).

Risperidone has been associated with the highest prevalence of SD of all SGA in both gender (Bitter et al., 2005; Ciudad et al., 2007; Fortier et al., 2003; Knegtering et al., 2008, 2004; Konarzewska et al., 2009; Montejo et al., 2010; Perez et al., 2008; Sathish Kumar and Sinha, 2015; Sechter et al., 2002; Tran et al., 1997; Ucok et al., 2007; Wang et al., 2016; Westheide et al., 2008; Wirshing et al., 2002) especially for daily doses above 4 mg/d (Peuskens, 1995).

High daily dose of risperidone were associated with increased PRL blood levels, which was associated with all domains increased SD. Palmitate paliperidone (the long-acting form of the derivative of risperidone, 9-hydroxy risperidone) was significantly associated with more SD than long-acting aripiprazole once-monthly [400 mg/M] (Potkin et al., 2017). However, one study reported that palmitate paliperidone induced lower PRL level than oral form, which was associated with SD improvement (Montalvo et al., 2013).

Amisulpride 400-1000 mg/d has been associated with a lower prevalence of SD than risperidone 4-10mg/d in one study (Sechter et al., 2002).

Switching to olanzapine has shown effectiveness for improving risperidone-induced or haloperidol-induced SD and was associated with a decrease of PRL blood levels (Ahl et al., 2004; Kim et al., 2002; Kinon et al., 2006). The risk of SD onset has been found to be increased in doses above 10 mg/day (Bobes et al., 2003).

Clozapine has not been associated to increased PRL blood levels (Mullen et al., 2001) and increased SD for clozapine have been reported for blood dosage above 250 mg/mL (Yusufi et al., 2007). Switch from FGA to clozapine was associated with improved sexual desire in both gender (Covington and Cola, 2000) and improved orgasmic function in male (Aizenberg et al., 2001).

Quetiapine has been associated with SD improvement including orgasm dysfunction and libido in both untreated SZ men and women (Atmaca et al., 2005), with no increased PRL blood level (Kelly and Conley, 2006; Westheide et al., 2008) and with improved risperidone-induced and haloperidol-induced SD after switch (Byerly et al., 2004; Nakonezny et al., 2007).

Aripiprazole has been associated with the lowest prevalence of SD of all antipsychotics and has shown improved SD after switching from all other antipsychotics in both gender (Chen et al., 2011; Fujioi et al., 2017; Hanssens et al., 2008; Jeong et al., 2012; Kirino, 2017; Knegtering et al., 2008; Knetering and De Boer et al., 2008; Mir et al., 2008; Raghuthaman et al., 2015; Sulejmanpasic-Arslanagic and Bise, 2017; Wang et al., 2016).

Two studies reported that antipsychotic polytherapy was associated with increased risk of SD (Bram et al., 2014; Yasui-Furukori et al., 2012).

4. DISCUSSION

The results of the present systematic review may be summarized as follows: a lot of studies have been carried out to explore the prevalence and risk factors of SD in subjects with schizophrenia with various quality and high heterogeneity in SD assessment. This heterogeneity explains the variation of SD prevalence ranking from 30 to 82% in both genders. Most of the studies have focused on treatment issues and have concluded that aripiprazole was the antipsychotic of reference in case of SD and that the risk of SD increased alongside with the daily dose and the antidopaminergic potency of the antipsychotic. PRL augmentation probably explains the association of antipsychotic-induced SD (Rettenbacher et al., 2010). The association between psychotic symptomatology and SD remains unclear, as symptoms have not been accurately explored. Major depression and addictive behavior have been poorly explored as well as other psychotropic

treatments. Other somatic comorbidities/chronic physical illnesses (like cardiovascular, neurological, inflammatory illnesses) have not been reported in most of the studies.

This review has shown that SZ subjects aged 18-70 years reported high rates of SD [30%-82%], all domains of sexual functioning being impacted. For SZ men the most frequently reported SD was erectile dysfunction [31%-95%] and for SZ women the loss of libido [31%-100%]. A mean prevalence cannot be directly calculated due to a high heterogeneity in study design and SD assessment, which is a limit of the present work. A future meta-analysis should be carried out in cross-sectional studies using validated standardized scales to evaluate SD. The SD rates reported by SZ subjects are higher than those of the general population ([40-50%] for women and [30%-50%] for men (DeRogatis and Burnett, 2008; Laumann et al., 1999; Lewis et al., 2010; McCabe et al., 2016; McCool, 2016; Rosen et al., 2000)). While no direct comparison can be carried out, the mean age of SZ subjects of the studies included in the present work was much younger than those of general population studies (around 30 years for SZ vs. over 50 years for people without SZ). **SZ subjects probably suffer from earlier SD than non-SZ populations due to illness, sociodemographic, and treatment issues.** No gender was found to be at increased risk of SD in observational studies (SZ men [33%- 85%]; SZ women [25%- 85%]). The women sample sizes were smaller than men due to the SZ sex ratio, which is usual in SZ studies.

Several explanations may be suggested for the high heterogeneity of these studies. Cultural/religious differences may influence sexual behavior and therefore the rate of SD in both general populations and SZ (Hocaoglu et al., 2014). The absence of validated questionnaire may explain some results with very low rate (until 3%) of SD in some studies (Xiang et al., 2011).

While SD increase alongside with age for men and is relatively stable in women in the general population (DeRogatis and Burnett, 2008; Hayes and Dennerstein, 2005; Kontula and Haavio-Mannila, 2009; Ucek et al., 2007), older age was associated with increased SD for both men and women in SZ populations (Hou et al., 2016; Mahmoud et al., 2012b; Malik et al., 2011; Smith et al., 2002). Relationship status was associated with SD in SZ subjects consistently with results suggesting that living with a sexual partner promoted better sexual functioning (Kontula and Haavio-Mannila, 2009; Sánchez-Fuentes et al., 2014). Only one study found an association between monthly income, working status and increased SD (Ucek et al., 2007). Higher education level has been found to be associated with higher risk for orgasmic dysfunction in SZ men, however being single may have been an important confounding factor in this study (Ong et al., 2014a). For SZ women positive symptoms have been found to be associated of increased SD (loss of libido, excitement and orgasmic dysfunctions) whereas, for SZ men, it was associated with lower orgasmic dysfunction and increased libido. These discrepancies may be due to different delusions types (e.g. persecutory vs. mystic or grandiosity) as well as to

excitement symptoms that may be found more frequently in men. However, there was no precision about specific positive symptoms in the studies, for example the delusion type. Depressive comorbidity was associated with SD in SZ subjects (Baldwin, 2001; Beck, 1967; Kovac et al., 2015; Porto, 2014), which is consistent with findings in non-SZ population (Chokka and Hankey, 2018).

Tobacco smoking was not associated with SD in SZ subjects, which is inconsistent with findings in non-SZ populations, especially for erectile dysfunction in men (Kovac et al., 2015) and vaginal lubrication and orgasmic dysfunction in women (Mehmet Ogur Yilmaz, 2015; Ucok et al., 2007). This absence may be explained by the mean young age of SZ subjects, while most of the tobacco-related SD appear beyond 40 years in mentally healthy populations (Biebel et al., 2016). Nicotine dependence and dose-effect remain also poorly explored to date and may impact this association (Ucok et al., 2007). These results may also be explained by the lowering of blood antipsychotic dose induced by tobacco smoking that may improve antipsychotic side effects including SD.

We confirmed that most of the studies focused on antipsychotic side effects (Zhang et al., 2001). While several mechanisms have been suggested to be implied in antipsychotic-induced SD (including antihistaminergic, antiserotonergic, antiadrenergic effects, peripheral cholinergic or antiadrenergic effects, and hyperprolactinemia) (Dervaux and Omari, 2005), the classification of antipsychotics by order of SD onset frequency clearly suggests that the antidopaminergic potency (inducing increased PRL) appears to be the most probable source of antipsychotic-induced SD in SZ subjects.

Antidepressant consumption has not been associated with increased SD in SZ subjects except for one study (Nakonezny et al., 2007) contrary to previous findings in non-SZ populations (Clayton et al., 2014; Higgins et al., 2010; Licitsyna O, 2011). This discrepancy may be explained by the co-prescription of antipsychotics that may “erase” the effect of antidepressants, given that most of the included SZ subjects treated by antidepressants were also treated by antipsychotics. As SD have been associated with major depression in SZ subjects, future studies should unravel the impact of depression and antidepressant on SD in SZ subjects.

4.1 Limits. Some studies reported non significant results that may be due to statistical power lack (Eberhard et al., 2007; Gao et al., 2017; Kikuchi et al., 2012; Nagaraj et al., 2009). Sociodemographic variables (age, educational, economical, professional status) and addictive behavior (especially alcohol and cannabis consumption) have been poorly explored. Chronic somatic illnesses (including sleep apnea, metabolic syndrome, cardiovascular disease, inflammatory illnesses) have been poorly explored while SZ subjects are at increased risk of somatic comorbidities. More specifically, chronic low-grade inflammation has been found in almost one third of the SZ subjects but its relationship with SD has never been explored to date. The high heterogeneity of studies due to the

use of miscellaneous validated and non-validated questionnaires, structured and non-structured interviews that made the results difficult to compare. Sexual orientation may be an important sociodemographic variable that may influence SD, however it has not been explored in most of the studies due to ethical concerns.

4.2 Strengths. The present work is the first systematic review on SD in SZ and has included 89 studies and 55424 participants, which provides a large view on the SD issue in SZ despite high heterogeneity.

4.3 Perspectives. Future studies should include systematic assessment of SD with a validated questionnaire. While amisulpride has been shown to increase PRL blood level, amisulpride-induced SD remain poorly explored to date (Serretti and Chiesa, 2011). The impact of long-acting vs. oral antipsychotics should be further evaluated. Beyond antipsychotic and antidepressant, the impact of other psychotropic drugs should be further studied. More specifically, anti-epileptic drugs, lithium and benzodiazepines could impact desire, erection and orgasm functions (Kaufman et al., 2018; Licitsyna O, 2011; Najafi et al., 2012).

Despite recent findings in SZ outpatients suggesting high rates of chronic physical illness, metabolic syndrome and chronic peripheral inflammation (Fond et al., 2018; Godin et al., 2015), their potential associations with SD have not been explored to date. The impact of lifestyle (diet, sleep and physical activity) on SD in SZ subjects has never been explored to date and may play a major role in SD onset.

5. Conclusion.

SZ subjects are at increased risk of SD compared to the general population in both frequency and earlier age at onset and SD may appear from the first psychotic episode. The present work has confirmed the role of antipsychotic drugs, especially those with high antidopaminergic potency, increased PRL and high daily dose. Diminishing the antipsychotic dose or switching to aripiprazole seems recommended in case of SD. However, other variables remain poorly explored including sociodemographic/lifestyle variables, addictive behavior, major depression, antidepressants and other psychotropic drugs, physical health issues including chronic illnesses, metabolic syndrome and chronic peripheral inflammation.

Conflicts of interest: no conflicts to disclose.

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