Structured review of the use of the Arizona sexual experiences scale in clinical settings

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Abstract

Background: Approximately 40% of women and 30% of men describe sexual dysfunction, although recognition in medical settings is suboptimal, due to problems in reporting and eliciting concerns relating to sexual function and satisfaction. Screening questionnaires may help to support this aspect of clinical practice. The Arizona sexual experiences scale (ASEX) includes items that quantify sex drive, arousal, vaginal lubrication or penile erection, ability to reach orgasm, and satisfaction from orgasm.

Method: We investigated the validity and other psychometric properties of the ASEX, and the findings from the populations in which it has been employed, by searching MEDLINE, EMBASE, and Google Scholar using the terms, Arizona sexual experiences scale, Arizona Sexual Experience Questionnaire, and ASEX. We eliminated duplications, letters, and papers not available in English, and grouped the remaining papers into the categories of psychometric, epidemiological, and outcome-based studies.

Results: After elimination of letters and duplicates, papers not in English, and preclinical and irrelevant studies, 104 papers were analyzed. The ASEX has excellent internal consistency, scale reliability and strong test–retest reliability. Analyses of variance reveal significant differences in total ASEX scores between patients and controls and between females and males. ASEX appears to be useful in a range of clinical situations including patients with primary sexual dysfunction, specific psychiatric disorders, specific physical illnesses, and treatment emergent sexual dysfunction.

Discussion: The ASEX appears to be a reliable instrument for identifying and quantifying sexual dysfunction across a range of populations in various clinical settings. Little is known about its utility in patients with anxiety disorders or relationships between ASEX scores and biological parameters.

Keywords
Arizona sexual experiences scale, ASEX, sexual dysfunction, sexual function
1 | BACKGROUND

Sexual dysfunction and sexual dissatisfaction are common: community surveys find that approximately 40% of women and 30% of men report troublesome sexual dysfunction. Low sexual desire (in women) and premature ejaculation (in men) are the most commonly reported sexual dysfunctions (Laumann, Paik, & Rosen, 1999; Moreira et al., 2005; Moreira et al., 2008). Sexual dysfunctions are closely associated with mental health problems, particularly depressive symptoms, but recognition of sexual dysfunction in primary care is low (Read et al., 1997; Nazareth et al., 2003; Cyranowski et al., 2004; Montejo et al., 2010). Sexual dysfunction increases the risk of depression by 130–200% (Atlantis & Sullivan, 2012; Clayton, El Haddad, Ilounakhamhe, et al., 2014) and 67% of depressed men and 75% of depressed women report problems relating to sexual function (Thakura, Singh, Bhattacharya, et al., 2012). A positive overall outcome for the patients with major depressive disorder is generally associated with a positive impact on sexual function, although most antidepressant drugs are associated with treatment-emergent sexual dysfunction in many patients (Clayton, Kornstein, Prakash, et al., 2007).

Assessment of sexual dysfunction can be challenging in practice, and differing assessment methods lead to varying findings. For example, an investigation found the prevalence of sexual dysfunction in men is 20% if reliant on spontaneous report by the patient, but 60% after direct enquiry (Segraves & Balon, 2014). Physicians may believe that the affected patients would spontaneously report sexual dysfunction (Clayton et al., 2014), but less than 20% who suffer from sexual dysfunction spontaneously report problems or seek help (Moreira et al., 2005; Moreira et al., 2008): "embarrassment" appears to be the main reason for not reporting (Nicolosi et al., 2006). The most reliable approach for assessing the prevalence and nature of sexual dysfunction is a comprehensive, integrated interview that considers multiple dimensions of sexual life (individual, relational, medical, erotic, sexual skill, and situational dimensions) (McCarthy, 2004), but this is time-consuming and often not feasible in practice.

Use of screening questionnaires may be valuable in busy clinical settings. Existing scales fall into different categories: general measures of sexual dysfunction, measures of sexual dysfunction in depressed populations, and female- and male-specific scales (Rizvi, Yeung, & Kennedy, 2011). A scale must demonstrate both reliability and validity in order to prove its acceptability for use. Tests of reliability estimate the ability of an instrument to generate consistent results under the same conditions, whereas tests of validity examine whether the instrument is actually measuring the concept in question (sexual function) and not a co-occurring construct (for example, anxiety) (Rizvi et al., 2011). Use of clinician-administered schedules may increase validity, but self-reporting scales have better reliability, possibly due to the sensitivity of the subject. Screening tools for sexual dysfunction with fewer items are more prone to false positive than false negatives, whereas questionnaires with more items have a better ability to examine specific domains of sexual functioning (Rizvi et al., 2011).

One of the more frequently used scales for assessing sexual functioning is the Arizona sexual experiences scale (ASEX). Its five items quantify sex drive, arousal, vaginal lubrication or penile erection, ability to reach orgasm, and satisfaction from orgasm. It is considered reliable and valid, and has been found concise and easy to administer in clinical settings (Baldwin, Manson, & Nowak, 2015; Clayton et al., 2014; Francois, Levin, Kutscher, et al., 2017; Khin, Kronstein, Yang, et al., 2015; Lorenz, Rullo, & Faubion, 2016; McGahuey, Gelenberg, Lakuves, et al., 2000). Possible total scores range between 5 and 30, higher scores indicating greater sexual dysfunction. ASEX designates "sexual dysfunction" when the total score is 19 or higher; or when any single item has a score of 5 or 6; or when any three items each have a score of 4 or higher (McGahuey et al., 2000). The ASEX has been used in many cross-sectional prevalence studies and in randomized controlled trials of pharmacological treatment, but there is some uncertainty about its utility in other clinical settings. We therefore aimed to examine the psychometric properties of the ASEX and its utility in assessing sexual dysfunction in clinical settings.

2 | METHOD

We conducted a computerized literature search of MEDLINE via Pub Med and EMBASE for all articles relating to use of the ASEX, published up to March 2018. We also included relevant articles which reported sexual dysfunction by searching Google Scholar. The terms employed were Arizona sexual experiences scale; Arizona Sexual Experience Questionnaire; ASEX. A combined list was generated and duplications were eliminated. All letters, and papers that were not available in English were eliminated.

We grouped the final dataset of publications into the broad categories of psychometric, epidemiological (concerned with establishing the prevalence of sexual dysfunction in particular populations), and outcome-based studies (concerned with the incidence of treatment-emergent sexual dysfunction during antidepressant or antipsychotic drug treatment).

3 | RESULTS

We identified 240 records: after excluding letters and duplicates, 228 were screened. Five were excluded as they were not in English, the remaining 223 were assessed for eligibility. From this group, 49 pre-clinical studies were excluded, and another 70 were excluded as they were either not obtainable or irrelevant. The final dataset included 104 papers (Figure 1). The specific features in each category are explained in detail below.

3.1 | Studies of psychometric properties

The search identified nine studies which examined psychometric properties (Briki et al., 2014; Byerly, Nakonezny, Fisher, Magouirk, & Rush, 2006; de Boer et al., 2013; Jitkritsadakul, Jagota, & Bhidayasiri, 2014; McGahuey et al., 2000; Nakhli et al., 2014; Nunes et al., 2009; Santos-Iglesias, Moyano, Castro, Granados, & Sierra, 2018; Soykan et al., 2004).
In order to establish its psychometric characteristics, the ASEX authors administered it to 107 control subjects (hospital employees, staff, residents, and faculty members) and 58 psychiatric patients. Female and male patients demonstrated higher scores on the ASEX (mean = 20.3 ± 4.8 and 17.2 ± 5.4, respectively) than did controls (mean = 13.5 ± 3.9 and 10.9 ± 2.6, respectively): in both groups, women scored higher than men. The ASEX had excellent internal consistency and scale reliability (Cronbach $\alpha$ = .9055) and strong test–retest reliability (patients, $r$ = .801, $p < .01$; controls, $r$ = .892, $p < .01$).

Analyses of variance (ANOVAs) revealed significant differences in total ASEX scores between patients and controls (males $F$ = 18.1, $p < .000$; females $F$ = 31.71, $p < .000$) and between females and males (patients $F$ = 5.22, $p = .026$; controls $F$ = 5.05, $p = .031$). Further ANOVAs revealed significant gender differences for patients on the ASEX items for drive and arousal ($F$ = 4.69, $p = .035$ and $F$ = 5.88, $p = .019$, respectively), with a trend on the item for ability to reach orgasm ($F$ = 3.72, $p = .059$). For controls, there were trends for gender differences on the items for drive, arousal, and ability to reach orgasm ($F$ = 3.57, $p = .067$; $F$ = 3.51, $p = .069$; and $F$ = 3.83, $p = .058$, respectively) (McGahuey et al., 2000). In further exploration by the authors, items on the ASEX correlated with factors and related items on the Brief Index of Sexual Functioning (BISF) (Taylor et al., 2005; Reynolds et al., 1988), but not with depression scores, on either the Beck Depression Inventory (BDI) (Beck, Steer, Ball, & Ranieri, 1996), or the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The accuracy of patient self-ratings of sexual dysfunction was verified with a four-item Gold Standard Clinician Rating scale (GSR), developed by the ASEX authors and administered during a semi-structured brief interview at each time interval. GSR scores correlated 100% with the patient’s belief of the presence of sexual dysfunction. The sensitivity and specificity of the ASEX at identification of sexual dysfunction were 82 and 90%, respectively, the positive predictive value was 88%.

**FIGURE 1** PRISMA flow chart of the literature review.
and negative predictive value was 85%. Receiver Operating Characteristic (ROC) analysis revealed an area under the curve (AUC) value of 0.929 ± 0.029. ROC analysis of the BISF revealed an AUC value of 0.786 ± 0.050. An independent area test revealed a significant difference between the two ROC curves (F = 2.4752, \( p = .0133 \)) (McGahuey et al., 2000).

In an investigation involving administration of the Turkish-language version of the ASEX to patients with end-stage renal failure (n = 43), it showed good internal consistency (Cronbach’s \( \alpha = .89 \)–.90) and test-retest reliability (\( r = .88, p < .001 \)). The convergent validity of the ASEX was measured by means of the correlation with the psychiatrists’ assessment for the presence of sexual dysfunction (\( r = .53, p < .001 \)). The results of ROC analysis for criterion validity revealed that ASEX scores could discriminate well (\( (0.85 ± 0.06) \) [95% confidence interval, 0.73–0.90]), \( p < .001 \)) between patients with “no sexual dysfunction” (n = 26) and with “sexual dysfunction” (n = 17). A total ASEX score of ≤11 was found to be the best cut-off point (sensitivity = 100%, specificity = 52%) for screening in this group of patients (Soykan et al., 2004). Another study in patients with MDD (n = 37) and healthy controls (n = 64), found Cronbach’s \( \alpha = .9451 \), a positive predictive value = 89.66%, a negative predictive value = 85.33%, a specificity = 95.31% and sensitivity = 70.27%, AUC = 0.8457, and an optimum cut off score of ≤18 (Briki et al., 2014).

A study involving administration of the ASEX to patients with either schizophrenia or schizoaffective disorder (n = 247), found a high degree of agreement between a single-item specific screening question for sexual dysfunction and the ASEX. Overall, the sensitivity (85%), specificity (63.7%), and positive (83%) and negative (67.1%) predictive values for the specific single-item screening question were deemed satisfactory by the authors. In contrast a single-item general side effect question performed rather poorly (sensitivity, 11.3%; specificity, 92.5%; positive predictive value, 76%; negative predictive value, 33%) (Byerly et al., 2006). Another study in patients with schizophrenia or schizoaffective disorder (n = 137) found a sensitivity of 80.8%, and specificity of 88.1% in relation to the Dickson Glazer Scale for the assessment of Sexual Function Inventory (DGSFI) (Dickson & Glazer, 2000) and AUC = 0.93, with an optimum cut off ASEX total score of 14/15 (Nunes et al., 2009).

Another study which administered the ASEX in patients with schizophrenia (n = 30) found that the correlation coefficients for calculating convergent validity were modest to good when compared with the Abbreviated Female Sexual Dysfunction Questionnaire (ASFQ) (Williams, Abraham, & Symonds, 2010; Williams, Edin, Hogue, Fehnel, & Baldwin, 2010), with the corresponding items on the Subject’s Response to Antipsychotics (SRA) questionnaire (Wolters, Kneetering, Wiersma, & van den Bosch, 2006) and with the ASEX (de Boer et al., 2013). A study which included administration of an Arabic-language version to patients with schizophrenia (n = 100), found Cronbach’s \( \alpha = .82 \) and satisfactory test–retest reliability (\( r = .92, p < 10^{-3} \)) (Nakhil et al., 2014).

In an investigation involving administration of the Thai-language version in patients with Parkinson’s disease (n = 40), a cut-off point of ≥16 points was found to represent a good threshold for sexual dysfunction (sensitivity 96.2%, specificity 92.9%). Reliability was documented with the Cronbach’s \( \alpha \) of all items at baseline and at 2-month follow-up, with values of 0.948 and 0.962 respectively. The Pearson’s correlation showed highly significant test–retest reliability for individual items (Item 1 \( r = .959 \) [\( p < .001 \)], Item 2 \( r = .914 \) [\( p < .001 \)], Item 3 \( r = .944 \) [\( p < .001 \)], Item 4 \( r = .992 \) [\( p < .001 \)], Item 5 \( r = .930 \) [\( p < .001 \)]), and for ASEX total score (\( r = .883, p < .001 \)) (Jitkristadakul et al., 2014).

A recent study using the Portuguese and Spanish versions of ASEX in healthy heterosexual participants (n = 118) found Cronbach’s \( \alpha = .73 \), sensitivity = 0.64–0.67, specificity = 0.72–0.80 for a cut off score of 15 (Santos-Iglesias et al., 2018).

### 3.2 Epidemiological studies

Many studies have employed the ASEX to ascertain the prevalence of comorbid sexual dysfunction in samples of patients with a range of psychiatric diagnoses (see Table 1) or physical health problems (see Table 2).

#### 3.2.1 Substance use disorders

The ASEX has been utilized in patients with alcohol and/or substance use disorders (Diehl et al., 2016; Dişiz et al., 2010; Gerra et al., 2016; Pendharkar et al., 2016; Venkatesh et al., 2014). In the first such study, 89.9% of women with alcohol and substance dependence (n = 126), were found to have ASEX-determined sexual dysfunction (Dişiz et al., 2010). In an investigation among treatment-seeking men with opioid dependence (n = 100), the prevalence of ASEX-determined dysfunction was found to be 48%, and there was strong correspondence with reported dysfunction in at least one of the domains of the International Index of Erectile Dysfunction (IIEF) (Rosen et al., 1997) (92%), and at least one of the domains of the Sexual Functioning Questionnaire Short-Form (CSFQ-14) (90%) (Venkatesh et al., 2014).

A cross-sectional study in women with substance-dependence (n = 213) utilized both the ASEX and non-standardized questions about sexual functioning, along with the Drug Abuse Screening Test (Skinner, 1982), the Short Alcohol Dependence Data questionnaire (Davidson & Raistrick, 1986), and the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991): there was a similar prevalence of sexual dysfunction using the two methods of enquiry (Diehl et al., 2016).

Patients undergoing long-term methadone treatment (n = 40), scored significantly higher than controls (n = 40) on the ASEX, the Care and Abuse-Questionnaire (CECA-Q) (Bifulco, Bernazzani, Moran, & Jacobs, 2005), and the Symptoms Check List 90 (SCL-90) (Derogatis & Cleary, 1977). ASEX scores were directly and significantly correlated with CECA-Q neglect score and SCL 90 psychiatric symptoms total score. Methadone dosages were not significantly correlated with sexual dysfunction scores, except for “erectile dysfunction,” for which an inverse association was seen. Plasma testosterone levels were significantly lower, but prolactin levels were significantly higher in cases than in controls: levels were significantly lower.
inversely correlated with ASEX scores, CECA-Q neglect scores, and psychiatric symptoms (SCL 90 score) among methadone patients. Prolactin levels were directly and significantly correlated with sexual dysfunction scores, psychiatric symptoms at SCL 90, and CECA-Q neglect scores. Neither testosterone nor prolactin levels were correlated with methadone dosage (Gerra et al., 2016).

In a case-control study in patients with alcohol dependence (n = 101), 58.4% of patients had ASEX-determined sexual dysfunction: the highest frequency of dysfunction according to individual items was for arousal (57.4%), followed by problems in desire (54.4%), erection (36.6%), satisfaction with orgasm (34.6%), and ability to reach orgasm (12.87%); patients and controls (n = 50), differed significantly in overall dyadic adjustment, in the domains of dyadic satisfaction and affective expression (Pendharkar et al., 2016).

### Depressive and anxiety disorders

Few studies have utilized the ASEX scale to determine sexual dysfunction in depressed patients (Dunlop et al., 2015; Montejo et al., 2011; Tekin et al., 2016; Williams et al., 2016).

In an early investigation, the prevalence of ASEX-determined dysfunction in patients with major depressive disorder (n = 514) was 73.4% (Montejo et al., 2011): ASEX scores were significantly associated with score on the Inventory of Depressive Symptomology, self-report version (IDS-SR) (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996), but not correlated with the Quality of Life Index (QMI) (Norton, 1983). An investigation in patients with social anxiety disorder (n = 113, of whom 30.1% had comorbid depression) found the proportion of ASEX-determined sexual dysfunction to be 36.3%: in addition, 36.3% of patients (n = 113) with social anxiety and sexual dysfunction, had a history of childhood physical abuse, and 14.2%, a history of childhood sexual abuse (CSA) (Tekin et al., 2016). In a further investigation of ASEX scores in patients with depression at baseline and 2 months follow up (n = 433), there were marked correlations between the Depression and Family Functioning Scale (DFFS) (Williams et al., 2016); the CGI-S (Zaider, Heimberg, Fresco, Schneier, & Liebowitz, 2003), the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), the Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959), the Sheehan Disability Scale (SDS) (Leon, Olsson, Portera, Farber, & Sheehan, 1997), the ASEX, the Patient Health Questionnaire-9 (PHQ-9) (Kroenke, Spitzer, & Williams, 2001), and the Work Productivity and Activity Impairment Questionnaire (WPAI) (Reilly, Zbrozek, & Dukes, 1993), (Williams et al., 2016). A further investigation which used two models to elucidate associations between symptoms and CSA found that depression severity and anxious arousal mediated the relationship between CSA and adult sexual function, and anxious arousal and sexual functioning mediated the association between CSA and depressive symptoms; when the models were

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### Table 1: ASEX-assessed sexual dysfunction and psychiatric diagnoses

| Study | N | Condition | Pharmacological treatment* | Results |
|-------|---|-----------|---------------------------|---------|
| Dişiz, Oskay, and Beji, 2010 | 126 F | Alcohol and substance misuse | Medication free | Elevated ASEX-reported dysfunction rates in women with alcohol and substance misuse compared to controls. |
| Montejo et al. 2011 | 514 | MDD | Medication free | ASEX-reported dysfunction in 73.4% of patients. |
| Venkatesh, Mattoo, and Grover, 2014 | 100 M 50 healthy controls | Substance misuse (opioid dependence) | Medication free | ASEX-reported dysfunction in 48% of patients with opioid dependence. |
| Dunlop et al. 2015 | MDD | Medication free | ASEX-reported dysfunction correlated with IDS-SR. |
| Gerra et al. 2016 | 40 M 40 healthy controls | Substance misuse | Long term methadone treatment | Childhood adversity and comorbid psychiatric symptoms contribute to sexual dysfunction and hormonal changes in methadone using patients. |
| Diehl, Rasool, dos Santos, Pillon, and Laranjeira, 2016 | 213 F | Substance misuse | Medication free | Similar prevalence of sexual dysfunction in women with substance misuse, using non-standardized questioning and ASEX. |
| Williams et al. 2016 | 142 M 336 F | MDD | Mixed group | Positive correlations between DFFS and the CGI-S, MADRS, HAM-A, SDS, ASEX, PHQ-9, and WPAI scores. |
| Pendharkar, Mattoo, and Grover, 2016 | 101 M | Substance misuse | Medication free | Sexual dysfunction prevalence of 58.4%. |
| Tekin et al. 2016 | 58 M 55 F | Social anxiety | Mixed group | ASEX-reported dysfunction in 36.3%. |
| Study                                    | N     | Condition          | Results                                                                 |
|------------------------------------------|-------|--------------------|--------------------------------------------------------------------------|
| Zhu et al. 2017                          | 47 M 28 F | Ostomy             | Mean ASEX score was 20.56 in patients with ostomy.                      |
| Soykan et al. 2005                       | 24 M 22 F | Hepatitis C        | ASEX-reported sexual dysfunction in 35%, more pronounced in fs (50%). GGT levels predicted ASEX-scores in chronic hepatitis C patients. |
| Yakoot and Salem, 2012                   | 66    | Hepatitis C        | ASEX scores were more improved in patients treated with Srulina than with Silymarin. |
| Eugenio, Jun, Cain, Jarrett, and Heitkemper, 2012 | 616 F | Irritable bowel syndrome | Women with ASEX-reported dysfunction were older and had a longer history of depression than those with without sexual dysfunction. |
| Oezdemir, Eryilmaz, Yurtman, and Karman, 2007 | 98    | Renal disease      | ASEX–determined dysfunction in 69.4% patients.                           |
| Hekmat et al. 2016                       | 140 F | Renal disease      | Significant correlations between total ASEX score and age and duration on haemodialysis. |
| Koca, Koca, and Ersoy, 2012              | 115 F 103 healthy controls | Renal disease | Higher ASEX-reported dysfunction with haemodialysis and peritoneal-dialysis compared to controls. |
| Kurdoglu, Usul Soyoral, Tasdemir, and Kurdoglu, 2012 | 47 F 20 healthy controls | Renal disease | Peritoneal-dialysis patients with depressive symptoms were 24 times more likely to develop ASEX-reported dysfunction. |
| Soykan et al. 2005                       | 25 M 18 F | Renal disease      | ASEX–determined dysfunction in 47% patients which did not improve with dialysis treatment. |
| Dikici et al. 2014                       | 246   | Renal disease      | ASEX scores were 24.6 ± 5.7 with comorbid restless legs syndrome and 22.5 ± 6.8 without. |
| Janse et al. 2017                        | 66 M 234 F | Hidradenitis suppurativa | ASEX-reported sexual dysfunction associated with poor quality of life and disease severity in F patients. |
| Kucukunal, Altunay, and Mercan, 2013     | 116 M 71 healthy controls | Genital warts | ASEX scores were significantly higher in M patients. |
| Mercan, Altunay, Demir, Akpinar, and Kayaoglu, 2008 | 31 neroudermatitis 24 psoriasis 33 controls | Various dermatological conditions | Higher ASEX-reported dysfunction with neurodermatitis than with psoriasis and controls. |
| Sukan and Maner, 2007                    | 100 F (50 vitiligo, 50 chronic urticaria) 50 healthy controls | Various dermatological conditions | Higher ASEX-reported dysfunction with vitiligo and urticaria than controls: Dysfunction more pronounced in fs. |
| Yilmaz et al. 2015                       | 74 M | Laryngeal cancer   | Significant increase in ASEX total scores correlated with age in patients who underwent laryngectomy. |
| Baboglu-Karaaltin, Binbay, Yigit, and Donmez, 2017 | 108 M 36 partial 72 total laryngectomy | Laryngeal cancer | Significant increase in ASEX total scores correlated with average scores on sexuality in patients who underwent laryngectomy. |
| Surbeck, Herbet, and Duffau, 2015        | 17 M 15 F | Glioma             | 53% reported sexual change after resection, with 44% ASEX-determined dysfunction. |
| Cleary, Hegarty, and McCarthy, 2011      | 106 F | Gynaecological malignancy | Higher ASEX scores 6 weeks after diagnosis. |
| Mathias et al. 2006                      | 20 F  | Breast cancer      | Bupropion treatment associated with reduction in ASEX scores.            |
| Senturk, Gollbasi, Kavlak, and Dilbaz, 2015 | 229 F | Post-menopausal symptoms | ASEX mean score 19.97, positively correlated with MRS scores. |
| Portman et al. 2014                      | 1.175 F | Post-menopausal symptoms | No change in ASEX-scores with paroxetine treatment. |
| Pinkerton, Bushmakin, Abraham, Cappelleri, and Komn, 2016 | 664 F | Post-menopausal symptoms | Improved ASEX-lubrication item scores with conjugated oestrogens/bazedoxifene administration. |
| Bachmann, Bobula, and Mirkin, 2010       | 652 F | Post-menopausal symptoms | Improved ASEX-vaginal lubrication item score, correlated with improved MENQOL and MS-TSQ scores. |
combined, anxious arousal was the most important mediator of CSA on depression, which in turn mediated associations with adult sexual satisfaction and relationship quality (Dunlop et al., 2015).

### 3.2.3 Gastrointestinal conditions and relevant interventions

Four investigations have included the ASEX in samples of patients with gastrointestinal and related conditions (Eugenio et al., 2012; Soykan et al., 2005; Yakoot & Salem, 2012; Zhu et al., 2017) (Table 3). A study of patients with chronic hepatitis C (n = 46), found a 35% overall prevalence of ASEX-reported sexual dysfunction, the prevalence being higher in women (50%): the most frequent problems in men were in drive (25%), arousal (17%), and erection (17%); in women, the most frequent problems were in drive (55%), arousal (50%), and reaching orgasm (59%). ASEX scores correlated significantly with age and education. After controlling for other variables, gamma glutamyl transpeptidase (GGT) levels predicted ASEX-scores (Soykan et al., 2005). Another study in patients with chronic hepatitis C (n = 66), who received dietary supplements, found that ASEX scores were more significantly improved with administration of *Spiroplina platensis* than with Silymarin (Yakoot & Salem, 2012). An investigation in women with irritable bowel syndrome (n = 616), randomized to comprehensive self-management or "usual care", found that those meeting ASEX criteria for sexual dysfunction were older, had higher lifetime depression and antidepressant use, more primary care visits, fewer mental healthcare visits, and greater sleep disturbance than those individuals without sexual dysfunction, but there was no significant group differences in gastrointestinal or somatic symptoms. When compared with "usual care" treatment, comprehensive self-management improved the sexual quality of life scores, with a weaker effect on ASEX scores (Eugenio et al., 2012). Finally, a prospective study found a mean total ASEX score of 20.56 among the patients undergoing ostomy surgery (n = 75): significant differences in ASEX score were observed in sub-groups relating to age, gender, educational level, family relations, operation modes, stoma type, operation time, complications, supporters, self-care ability, and sexual life guidance. Multiple stepwise regression analysis indicated that family relations, operation modes, ostomy type, complications, and sexual life guidance all affecting sexual experience (Zhu et al., 2017).

### Table 2 (Continued)

| Study | N | Condition | Results |
|-------|---|-----------|---------|
| Veras, Bruno, de Avila, and Nardi, 2011 | 88 F | Polycystic ovarian syndrome | Negative correlation between ASEX score and testosterone, luteinizing hormone and dehydroepiandrosterone sulfate level. |
| Kovalovsky et al. 2010 | 36 | Healthy women using LNG-SI | No change in ASEX scores following treatment with duloxetine. |
| Jitkritisadakul, Jagota, and Bhidayasiri, 2015 | 35 M, 25 F 60 controls | Parkinson’s disease | ASEX-determined sexual dysfunction prevalence of 81.6%. |
| Özcan et al. 2015 | 89 (M:F = 1.87) | Parkinson’s disease | UPDRS motor score correlated with erection/lubrication, HAMD score with orgasm satisfaction, HAMA score with stimulation and orgasm. |
| Celikel, Ozel-Kizil, Akbostanci, and Cevik, 2008 | 45 patients 45 controls | Parkinson’s disease | Female patients had reduced sexual drive and less orgasm satisfaction, M patients reported easier orgasms than controls. |
| Celik et al. 2013 | 45 M 44 F | Multiple sclerosis | Female patients reported ASEX-arousal dysfunction significantly more frequently than M patients. |
| Gül et al. 2013 | 50 patients 50 controls | Behçet’s disease | ASEX scores, HDRS, HARS and GRISS were significantly higher in patients with Behçet’s disease. |
| Eyada and Atwa, 2007 | 34 F | Myocardial infarction | Non-ST-elevation myocardial infarction associated with elevated ASEX-reported non-satisfaction and reduced drive. |
| Hoffman et al. 2010 | 46 M | Cardiovascular risk | ASEX scores were predicted by the greater Framingham risk score and lower FMD, but not by BDI scores. |
| Kaya Erten, Zincir, Ozcak, Selcuk, and Elmali, 2014 | 38 F | Diabetes mellitus | ASEX-determined prevalence of dysfunction in 47.4%. |
| Copuroglu et al. 2017 | 40 M | Pelvic fractures | ASEX-determined 10% prevalence of dysfunction following surgery after excluding vascular, neural and urogenital system pathologies. |
| Bestepe et al. 2011 | 74 patients 30 controls | Persistent headache | ASEX subscales: 1, 2, 3 and 4 were significantly higher in patients with migraines than in controls. |
| Study                          | N  | Condition | Pharmacological treatment | Results                                                                                                                                 |
|-------------------------------|----|-----------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Gelenberg et al. 2000         | 19 | MDD       | Mirtazapine               | On switching to mirtazapine, 58% of patients reported the return of normal sexual functioning, and 11% reported a significant improvement in sexual functioning, in patients with MDD. |
| Masand et al. 2001            | 30 | MDD       | Bupropion                 | Augmentation with bupropion had no significant advantage over continuation on ssris, without augmentation, in reducing ASEX-scores.       |
| DeBattista, Solvason, Poirier, Kendrick, and Loraas, 2005 | 41 | MDD       | Bupropion                 | Augmentation with bupropion had no significant advantage over continuation on ssris, without augmentation, in reducing ASEX-scores.       |
| Atmaca, Kuloglu, Tezcan, and Buyukbayram, 2003 | 23 | MDD       | Tianeptine                | Switching to tianeptine resulted in a significant difference in ASEX scores between baseline and week 4 or week 8, in patients with MDD.       |
| Detke et al. 2004             | 256| MDD       | Paroxetine, duloxetine    | The incidence of ASEX-reported treatment emergent sexual dysfunction was 46.5% with duloxetine and 62.8% with paroxetine, in patients with MDD. |
| Baldwin, Cooper, Huusom, and Hindmarch, 2006 | 232| MDD       | Citalopram, paroxetine    | Slight increase in ASEX-scores during acute treatment with paroxetine or escitalopram, ASEX scores decreasing during longer-term treatment, in patients with MDD. |
| Perahia, Wang, Mallinckrodt, Walker, and Detke, 2006 | 119 M 237 F | MDD | Paroxetine, duloxetine and placebo | Non-inferiority of duloxetine versus paroxetine in ASEX-determined sexual dysfunction in patients with MDD.                                |
| Zourková, Cesková, Hadasová, and Ravcuková, 2007 | 55 | MDD       | Paroxetine                | Higher ASEX-determined dysfunction with paroxetine in MDD, F patients with poor CYP2D6 phenotype.                                   |
| Baldwin, Hutchison, Donaldson, Shaw, and Smithers, 2008 | 84 M 2018 F | MDD | Vml-670                   | Augmentation with VML-670 has no significant advantage over placebo in reducing ASEX-scores in patients with SSRI-associated sexual dysfunction. |
| Dording et al. 2008           | 3 M 17 F | MDD | Maca 3.0 g/day a Peruvian plant | Improvement in ASEX-scores with Maca root preparation, in patients with MDD.                                                              |
| Pae et al. 2009               |    | MDD       | Methylphenidate           | Augmentation with methylphenidate had no significant advantage over continuation on ssris, without augmentation, in reducing ASEX-scores. |
| Rickels et al. 2009           | 410| MDD       | Vilazodone                | Treatment associated with no clinically significant differences in ASEX scores for either gender at the end of treatment.               |
| Khan, 2009                    |    | MDD       | Vilazodone                | No significant difference between placebo and vilazodone in ASEX reported sexual dysfunction.                                            |
| Kennedy, 2010                 | 523| MDD       | Flibanserin               | 70% of patients with sexual dysfunction at baseline reported an improvement in sexual function, in patients with MDD.                 |
| Williams, Edin, et al. 2010   | 207 M 497 F | MDD and anxiety disorders | Various psychotropics     | The prevalence of ASEX-reported antidepressant-emergent sexual dysfunction was 46.4% in Ms and 52.1% in fs.                            |
| Dueñas et al. 2011            | 1,647 | MDD       | Duloxetine                | ASEX-reported dysfunction at 6 months treatment with duloxetine of 23.4%, comparable to that with 28.7% with ssris, in patients with MDD. |
| Montejo et al. 2011           | 514 | MDD       | Various antidepressants   | Probability of treatment-emergent sexual dysfunction of 49.6% in non-responders and 33.2% in responders for patients with MDD.           |
| Calandra, Russo, and Luca, 2012 | 30 | MDD       | Bupropion, Sertraline     | Bupropion effective in reducing weight and improving ASEX scores, in patients with MDD comorbid with binge eating disorder.          |
| Study                                    | N      | Condition               | Pharmacological treatment               | Results                                                                 |
|-----------------------------------------|--------|-------------------------|-----------------------------------------|-------------------------------------------------------------------------|
| Liang, Ho, Chiang, and Su, 2012         | 56     | MDD                     | SSRI or venlafaxine                    | 5-HT-2A receptor −1,438 AA genotype was significantly over-represented in patients with MDD experiencing sexual dysfunction. |
| Sapetti, 2012                           | 25     | MDD                     | Agomelatine                            | Improvement in ASEX scores in women after switching to agomelatine treatment, in patients with MDD. |
| Lin, Juang, Wen, Liu, and Hung, 2012    | 70     | MDD                     | Venlafaxine                            | 4 weeks venlafaxine treatment improved anxiety, depression, somatic symptoms (IP = 48.5%–26.0%), and total ASEX-CV score (IP = -1.6%), in patients with MDD. |
| Clayton, Reddy, Focht, Musgnung, and Fayyad, 2013 | 422    | MDD                     | Desvenlafaxine                         | No significant negative effect on ASEX-assessed sexual function over 12 weeks of treatment with desvenlafaxine, with the exception of orgasmic dysfunction in men without pre-existing sexual dysfunction. |
| Clayton et al. 2015                     | 909    | MDD                     | Desvenlafaxine                         | No difference between desvenlafaxine and placebo in ASEX-determined sexual dysfunction in patients with MDD. |
| Mahableshwarkar, Jacobsen, Chen et al. 2015 | 469    | MDD                     | Vortioxetine                           | No significant difference in ASEX scores between vortioxetine and placebo in patients with MDD. |
| Genek Ülgen and Güleç, 2016             | 82     | MDD and anxiety disorders | Various psychotropics                  | Baseline prevalence of ASEX-reported dysfunction in patients with depression and anxiety was 69.5%: 42.11% of whom showed no sexual impairment after taking antidepressants. Incidence of treatment emergent dysfunction with antidepressants = 32%. |
| Han et al. 2015                         | 101    | MDD                     | Various antidepressants                | Aripiprazole augmentation and antidepressant switching had comparable effect on sexual dysfunction, as assessed by ASEX scores, in patients with MDD. |
| Tufan, Ozten, Isik, and Cerit, 2013      | 33     | MDD                     | Various SSRI                           | Prevalence of ASEX-reported sexual dysfunction was 73.7% with ssris and 85.7% of treatment-free controls, with MDD. |
| Mahableshwarkar, Jacobsen, and Chen, 2013 | 611    | MDD                     | Vortioxetine, duloxetine               | 46.9%, and 33.3% with vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine and placebo, respectively, in patients with MDD. |
| Westenberg, Stein, Yang, Li, and Barbato, 2004 | 300    | Social anxiety disorder | Fluvoxamine                            | No ASEX-reported difference between fluvoxamine and placebo in patients with generalized social anxiety disorder. |
| Schutters, van Megen, Van Veen, Schruers, and Westenberg, 2011 | 21     | Social anxiety disorder | Paroxetine, Mirtazepine                | The prevalence of ASEX-determined dysfunction in GAD was 50% for patients treated with paroxetine plus placebo, and 38% of patients treated with paroxetine plus mirtazapine, in patients with GAD. |
| Márquez, Arenoso, and Caruso, 2011       | 190    | Panic disorder           | Alprazolam                             | ASEX scores showed no improvement with alprazolam for acute panic disorder. |
| Mahableshwarkar, Jacobsen, Chen, and Simon, 2014 | 781    | GAD                     | Vortioxetine                           | No difference between vortioxetine and placebo in ASEX, in patients with GAD. |
| Sarris et al. 2013                      | 37 M   | GAD                     | Kavalactones (Piper methysticum)       | Kavalactone significantly improved drive in medication free women with GAD. |
3.2.4 | Renal disease

The ASEX has been included in a series of investigations of patients with renal disease (Dikici et al., 2014; Hekmat et al., 2016; Koca et al., 2012; Kurdoglu et al., 2012; Ozdemir et al., 2007; Soykan et al., 2005). A point prevalence study in patients with end-stage renal disease (n = 98) determined that 69.4% had ASEX-defined sexual dysfunction (Ozdemir et al., 2007). In a longitudinal investigation among end stage renal disease patients, who had undergone dialysis treatment for at least 12 months (n = 43), ASEX-defined sexual dysfunction was present in 47% at baseline and 42% at 6-month follow-up, and total and item-by-item ASEX scores did not change significantly during this period: in female patients, HDRS (Hamilton, 1960) scores were significantly higher in patients with ASEX-reported sexual dysfunction, both at baseline assessment and at follow-up (Soykan et al., 2005). A study of female patients undergoing long-term haemodialysis (n = 140) found significant correlations between total ASEX score, age and duration of haemodialysis, though no correlation between serum haemoglobin, parathyroid hormone, creatinine, iron, calcium, phosphorus, and urea reduction ratio and the ASEX score: there was also a significant difference in total ASEX score between cases and controls (Hekmat et al., 2016). Another investigation in haemodialysis patients (n = 246) found higher ASEX scores among patients with comorbid restless legs syndrome (RLS) than those without RLS, and significant relationships between ASEX scores and demographic variables including educational achievements, occupation, and marital status (Dikici et al., 2014). An investigation in female patients who underwent renal replacement therapy found that ASEX-determined sexual dysfunction rates were significantly higher in a haemodialysis group (n = 39) compared to the peritoneal dialysis group (n = 43) and the kidney transplant group (n = 33), and sexual dysfunction rates were higher in kidney transplant and dialysis patients when compared with controls: multivariate analysis indicated that marital duration and haemodialysis were independent risk factors for sexual dysfunction in the renal replacement population (Koca et al., 2012). A further investigation found that total ASEX scores, ability to reach orgasm, and BDI scores were significantly higher among peritoneal-dialysis (n = 22) and haemodialysis (n = 25) patients than controls (n = 30): peritoneal-dialysis patients with depressive symptoms were 24 times more likely to experience sexual dysfunction than those without depression, and serum FSH and LH levels were positively correlated with arousal and erection/lubrication scores in the depressed peritoneal-dialysis patients (Kurdoglu et al., 2012).

3.2.5 | Dermatological conditions

The ASEX has been used to ascertain the point prevalence of sexual dysfunction in a range of dermatological conditions (Sukan & Maner, 2007; Mercan et al., 2008; Kucukunal et al., 2013; Janse et al., 2017). An early investigation in female patients with vitiligo (n = 50) or chronic urticaria (n = 50) found that ASEX total scores were significantly higher than in controls (n = 50): sexual drive and satisfaction item scores were significantly lower in both patient groups, female patients had more dysfunction in reaching orgasm, and male patients reported less orgasm satisfaction (Sukan & Maner, 2007). A healthy-control study in patients with neurodermatitis (n = 31) or psoriasis (n = 24) found that neurodermatitis patients reported more sexual (ASEX-defined) and depressive symptoms (assessed with the BDI), than patients with psoriasis or healthy controls (n = 33) (Mercan et al., 2008). An investigation in patients with hidradenitis suppurativa (n = 300) found that female sex and later age of onset were both associated with poor sexual function: poor quality of life was associated with analgenital involvement, early age of onset, and disease severity; whereas sexual health was positively associated with quality of life in female but not male patients (Janse et al., 2017). Finally, ASEX scores were significantly higher in male patients with genital warts (n = 116) than controls (n = 71), there being positive correlations between BDI and BAI scores with ASEX total and item scores (Kucukunal et al., 2013).

3.2.6 | Malignancies

A series of investigations of sexual function have employed the ASEX to assess sexual function among groups of patients with various forms of malignancy (Mathias et al., 2006; Cleary et al., 2011; Yilmaz et al., 2015; Batoglu-Karaaltin et al., 2017; Surbeck et al., 2015). A descriptive, correlational study in women with reproductive system malignancies (cervical, ovarian, endometrial, and vulvar) (n = 106), found higher ASEX scores 6 weeks post-diagnosis (Cleary et al., 2011). An investigation in patients with laryngeal carcinoma (n = 74) found that ASEX scores in total or partial laryngectomy patients were not significantly different (13.98 ± 6.32 and 13.08 ± 4.96, respectively), though mean BDI scores were significantly higher in total laryngectomy patients (13.20 ± 10.41 vs. 7.76 ± 8.14): BDI scores correlated with Rosenberg Self-Esteem Scale (RSES) (Rosenberg, 1965) scores, and ASEX scores correlated with age (Yilmaz et al., 2015). In a second investigation in patients with laryngeal carcinoma patients, 90.3% of total laryngectomy patients and 63.9% of partial laryngectomy patients had experienced negative effects on sexual function, and ASEX scores were correlated with average scores on the sexuality sub-unit (QL-35 59–60) of the Cancer and Head and Neck module (Sherman et al., 2000), (Batoglu-Karaaltin et al., 2017). An investigation in patients who underwent surgical resection for diffuse low-grade glioma (n = 32) found that ASEX-determined sexual dysfunction was present in 44% of patients (60% of women, 29% of men), and 53% reported post-operative changes in sexual function (with deterioration in 88%, but improvement in 12%). Right-sided resections were associated with more dysfunction in reaching orgasm than left-sided resections, temporal lobe resection was linked to lower sexual drive and sexual arousal in men than in women, and continued antiepileptic drug treatment in patients who underwent right-sided resection was associated with higher ASEX scores in men than women (Surbeck et al., 2015). An investigation of the effects of 8 weeks of bupropion (150 mg/day) treatment on sexual function in breast cancer patients who had
undergone chemotherapy but were currently receiving radiotherapy \((n = 20)\) found mean ASEX scores declined from 23.45 at baseline to 18.95 at endpoint (Mathias et al., 2006).

### 3.2.7 Non-malignant gynaecological or post-menopausal conditions

A number of studies have employed the ASEX to assess sexual dysfunction in patients with a range of conditions, (Kovalevsky et al., 2010; Bachmann et al., 2010; Veras et al., 2011; Portman et al., 2014; Senturk et al., 2015; Pinkerton et al., 2016). An investigation in women with polycystic ovarian syndrome \((n = 88)\) found a mean ASEX score of 14.4 and an overall prevalence of sexual dysfunction of 13.3% with negative correlations between the ASEX scores and the levels of total testosterone, luteinizing hormone and dehydroepiandrosterone sulfate (Veras et al., 2011). An investigation among postmenopausal women \((n = 229)\) found a mean ASEX score of 19.97, with a positive correlation to the mean total score on the Menopause Rating Scale (Hauser, Huber, Keller, Lauritzen, & Schneider, 1994), (Senturk et al., 2015). In a randomized, double-blind, placebo-controlled study involving post-menopausal patients with symptoms of moderate or severe vulvar and/or vaginal atrophy \((n = 652)\), treatment with bazedoxifene /conjugated oestrogens was associated with a significantly greater improvement from baseline to endpoint in ASEX lubrication item score from baseline, when compared with placebo (but with no significant difference in change in total ASEX score). There were also significant advantages over placebo in vasomotor function, sexual function and total scores on the Menopause-Specific Quality of Life questionnaire (QLS) (Hilditch et al., 1996) and in satisfaction with treatment, satisfaction with control of hot flushes, quality of sleep, and mood or emotions on the Menopause Symptoms Treatment Satisfaction Questionnaire (Bachmann et al., 2010; Hill, Fehnel, Bobula, Yu, & McLeod, 2007). A randomized, double-blind, placebo-controlled investigation in non-hysterectomized post-menopausal women \((n = 664)\) which also involved conjugated oestrogens/bazedoxifene found that at baseline, 52% reported pain with intercourse, 35% vaginal dryness and 13% vaginal itching/irritation as bothersome symptoms: at the end of treatment, there was a significant reduction in ASEX-lubrication sub-score in those with pain at intercourse, and significant improvements in vaginal cell counts in women with dryness or pain at intercourse as their most bothersome symptom (Pinkerton et al., 2016). A large randomized double-blind, placebo-controlled study \((n = 1,174)\) found no clinically or statistically significant changes in ASEX-scores from baseline in the paroxetine 7.5 mg treatment group (Portman et al., 2014). A prospective randomized double-blind study in women using a levonorgestrel subcutaneous implant (LNG-SI), who were treated with doxycycline (20 mg) or placebo, found no differences in ASEX-scores changes between the placebo and doxycycline groups (Kovalevsky et al., 2010).

### 3.2.8 Neurological conditions

The ASEX has been used to determine the prevalence of sexual dysfunction in patients with Parkinson’s disease (Celikel et al., 2008; Jitkritisadakul et al., 2015; Özcan et al., 2015) and multiple sclerosis (Celikel et al., 2013). A case-control study among patients with Parkinson’s disease \((n = 45)\) found that female patients had reduced sexual drive and were less satisfied with orgasm than controls, whereas male patients reported easier orgasms than controls: regression analysis identified increased age and female sex as predictive of reduced sexual drive and sexual arousal (Celikel et al., 2008).

In an investigation of sexual function which found the point prevalence of ASEX-determined dysfunction to be 81.6% in Parkinson’s patients \((n = 60)\) compared to 48.3% of controls, ASEX score was correlated with disease severity and depressive symptoms: logistic regression analysis found factors related to sexual dysfunction included absence of recent sexual intercourse, postural instability, and HAMD item 14 (sexual symptoms) (Jitkritisadakul et al., 2015). In a separate investigation in patients with Parkinson’s disease \((n = 89)\) which found a mean ASEX total score of 18.54 (SD ±7.27), ASEX total scores were correlated with age, disease stage and HAMA scores: there was no correlation between disease duration and ASEX item scores, but motor symptom scores were correlated with dysfunction in erection or lubrication, HAMD score with orgasm dissatisfaction, and HAMA score with dysfunction in stimulation and orgasm (Özcan et al., 2015). An investigation of sexual function among patients with multiple sclerosis \((n = 89)\) found that women reported ASEX-arousal difficulties significantly more than frequently than men (7.9% versus 1.1%); women also had significantly higher scores on the Multiple Sclerosis Intimacy and Sexual Questionnaire-19 (MSISQ-19) (Sanders, Foley, & LaRocca, 2000) than men (42.6 ± 12.9 vs. 36.6 ± 13.3) (Celik et al., 2013).

### 3.2.9 Cardiovascular function

In a study in male patients with major depressive disorder \((n = 46)\), regression analysis indicated that ASEX scores were predicted by greater Framingham risk score and lower flow-mediated dilation of the brachial artery (FMD), but not by BDI scores: erectile dysfunction, measured by ASEX item 3, was associated with greater risk of cardiovascular disease and impaired vascular endothelial function, suggesting cardiovascular risk factors may adversely affect erectile function through impairment of vascular endothelial function (Hoffman et al., 2010). Two investigations have employed the ASEX to determine the point prevalence of sexual dysfunction in patients with cardiovascular disease (Eyada & Atwa, 2007; Kaya Erten et al., 2014). A limited study in female patients with non-ST-elevation myocardial infarction \((n = 34)\) found high levels of reported sexual non-satisfaction and reduced sexual drive (Eyada & Atwa, 2007). In a sample of women with diabetes mellitus \((n = 38)\), in which 47.4% expressed problems with sexual relationships, ASEX total score was correlated with the type of hypoglycaemic treatment, duration and complications of illness, spousal relationship, HbA1c level and blood pressure (Kaya Erten et al., 2014).

### 3.2.10 Other medical conditions

In male patients with a pelvic fracture \((n = 40)\) but without consequent vascular, neural or urogenital problems, sexual dysfunction was
The ASEX-determined dysfunction at baseline, with a slight increase in ASEX scores above baseline values during acute treatment in both groups, but a subsequent slight decline below baseline values towards the end of maintenance treatment (Baldwin et al., 2006). A randomized, placebo-controlled study in patients with major depressive disorder (n = 410), found no significant differences in ASEX scores between patients allocated to vilazodone or placebo, in men or women (Rickels et al., 2009); these findings being repeated in a further study, that found no significant difference between placebo and vilazodone in ASEX-defined sexual dysfunction (Khan, 2009).

A cross-sectional survey investigated the impact of sexual dysfunction in patients receiving antidepressant treatment (n = 704) in three European countries. ASEX scores generally exceeded the threshold defining sexual dysfunction: 67.2% in the German, 79.4% in the Spanish, and 73.3% in the Dutch samples. The prevalence of antidepressant-associated sexual dysfunction was conservatively estimated to be between 37.1% (German sample) and 61.5% (Spanish sample). Overall, 46.4% of male and 52.1% of female participants were classified as having antidepressant-associated sexual dysfunction (Williams, Abraham, & Symonds, 2010; Williams, Edin, et al., 2010).

A 12-week double-blind, randomized placebo-controlled study of desvenlafaxine (50 mg/day) in patients with major depressive disorder (n = 422) found no significant adverse effect on sexual function (with the exception of orgasmic dysfunction in men without pre-existing sexual dysfunction). Greater orgasmic dysfunction at Week 12 was observed in the sub-group of men without baseline sexual dysfunction treated with desvenlafaxine, relative to placebo. Conversely, women without baseline sexual dysfunction experienced poorer overall sexual functioning and orgasm satisfaction at Week 12 with placebo, compared to desvenlafaxine. Sub-group analyses of treatment responders and non-responders found no difference in the proportion of men or women who developed or had resolution of sexual dysfunction in the desvenlafaxine and placebo groups (Clayton et al., 2013). In a further analysis of the incidence of sexual dysfunction during desvenlafaxine treatment, rates of ASEX-determined dysfunction were comparable with different doses of desvenlafaxine, and comparisons for desvenlafaxine versus placebo of change from baseline in ASEX total score and individual item scores were not significantly different, neither was there a significant treatment-by-gender interaction (Clayton et al., 2015).

A small study in patients with major depressive disorder (n = 33) receiving SSRI or placebo found a prevalence of ASEX-determined dysfunction of 73.7% with SSRIs and 85.7% with treatment-free controls, but no significant differences between groups: dysfunction was associated with female gender, regardless of treatment (Tufan et al., 2013). A survey in patients with depressive and anxiety disorders (n = 82), found 69.50% had been diagnosed with sexual dysfunction prior to antidepressant treatment: after 3 months of treatment, 24 patients in this group (42.1%) showed no impairment on ASEX scores, whereas scores in 33 patients (57.9%) still indicated dysfunction. By contrast, eight of the 25 patients (32%) who were not diagnosed with sexual dysfunction prior to treatment were later...
diagnosed with sexual dysfunction. The presence of dysfunction correlated with patients' level of functioning, independent of anxiety and depressive symptoms (Genek Ülgen & Güleç, 2016).

An 8-week randomized placebo-controlled study of vortioxetine in patients with major depressive disorder (n = 469) found that ASEX total scores during treatment were similar, with no significant differences in depressive symptoms (Mahableshwarkar, Jacobsen, Chen, et al., 2015; Mahableshwarkar, Jacobsen, Serenko, et al., 2015). In a comparison of vortioxetine (2.5 or 5.0 mg), duloxetine (60 mg) and placebo, rates of ASEX-determined sexual dysfunction were 51.0%, 37.5%, 46.9%, and 33.3% in the vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine, and placebo groups, respectively (Mahableshwarkar et al., 2013).

Antidepressant drugs are often used in patients with diagnoses other than depressive illness. A double-blind placebo-controlled study of fluvoxamine controlled-release in patients with generalized social anxiety disorder (n = 300), found that fluvoxamine did not cause ASEX-determined sexual dysfunction (Westenberg et al., 2004). In patients with generalized anxiety disorder, sexual dysfunction was present in 50% of patients with treated paroxetine when combined with placebo, compared to 38% of patients treated with paroxetine when combined with mirtazapine (Schutters et al., 2011). A double-blind randomized, controlled study of sublingual alprazolam tablets in acute treatment of patients (n = 190) with panic disorder found that there was no improvement in ASEX scores, despite improvements in scores on the Clinical Global Impressions (CGI-S/CGI-I) (Guy 1976; Busner & Targum, 2007), HAMA, Patient Global Impression (PGI) (Guy, 1976), Psychological General Well-Being Index (PGWBI) (Dupuy, 1984), and Panic Disorder Severity Scale (PDSS) (Shear et al., 1997) (Márquez et al., 2011). In a retrospective cohort study in patients with comorbid binge eating disorder and major depressive disorder, bupropion was superior to sertraline in reducing weight and improving ASEX scores (Calandra et al., 2012). In a double-blind, randomized placebo-controlled study in patients (n = 781) with primary generalized anxiety disorder, rates of treatment-emergent sexual dysfunction in vortioxetine-treated groups were similar to those with placebo (Mahableshwarkar et al., 2013).

A study which utilized the Chinese version of the ASEX in patients with MDD (n = 70), found that HADS-D scores were strongly correlated with ASEX scores. Four weeks of open-label treatment with venlafaxine improved depressive, anxiety and somatic symptoms (improvement percentage (IP) = 48.5–26%) and ASEX total score (IP = −1.6) (Lin et al., 2012).

Some studies have employed the ASEX to investigate the management of sexual dysfunction in patients receiving antidepressants. Switching to tianeptine (n = 23) resulted in a significant difference between baseline and week 4 or week 8 in ASEX scores, associated with significant improvement in HAM-D scores (Atmaca et al., 2003). A 6-week randomized controlled trial (n = 101) found that aripiprazole augmentation and antidepressant switching had comparable effect on sexual dysfunction, as assessed by ASEX scores (Han et al., 2015). Switching to agomelatine in patients with acute depressive episodes (n = 25) led to improved ASEX scores after 3 weeks of treatment (mainly in women rather than men); visual analogue scales for desire, arousal, time, and intensity of orgasm and vaginal lubrication showed improvement in all stages of sexual response in women, with minimal changes in men, and treatment was associated with reduction in depressive symptoms (Sapetti, 2012). The 5-HT1A agonist and 5-HT2A antagonist flibanserin was found to be associated with low rates of ASEX-reported treatment-emergent sexual dysfunction in women with major depressive disorder (n = 523); 70% of flibanserin-treated women with baseline sexual dysfunction reported an improvement in sexual function, compared with 30% of placebo-treated women (Kennedy, 2010). Switching to mirtazapine (open-label) for up to 6 weeks (n = 19), led to a return of normal sexual functioning (assessed by ASEX) in 58% of patients, and 11% reported a significant improvement in sexual functioning (Gelenberg et al., 2000). Treatment augmentation with Maca 3.0 g/day (a Peruvian plant), (n = 20) had a significant improvement in ASEX and Massachusetts General Hospital Sexual Function Questionnaire (MGH-SFQ) (Dording et al., 2008). Augmentation with VML-670 (a 5-HT1A receptor agonist), (n = 88) conferred no significant advantage over placebo (Baldwin et al., 2008). Augmentation with bupropion (n = 41) (DeBattista et al., 2005), (n = 30) (Masand, Ashton, Gupta, & Frank, 2001) or methylphenidate (Pae et al., 2009), also had no significant advantage on ASEX-scores. A placebo controlled trial investigated the use of kavalactones in patients with generalized anxiety disorder (n = 75). Kavalactone administration significantly increased ASEX-sexual drive scores in female participants when compared to placebo, with no negative effects seen in male participants: and there was a highly significant correlation between ASEX reduction (improved sexual function and performance) and anxiety reduction in the whole sample (Sarris et al., 2013).

An investigation involving drug-naïve patients with major depressive disorders (n = 56), found that the 5-HT2A receptor −1,438 AA genotype was significantly over-represented among the sub-group of patients who experienced sexual dysfunction during SSRI or venlafaxine monotherapy: mean baseline HAMD-17 score, mean baseline ASEX score, and mean end-point ASEX score were all significantly higher than in patients without sexual dysfunction, although mean end-point HAMD-17 scores did not differ significantly between groups (Liang et al., 2012). Another study in patients with paroxetine-induced sexual dysfunctions (n = 55), found a significantly higher rate of ASEX-determined dysfunction among females with a "poor" metabolic status-CYP2D6-phenotype (Zourková et al., 2007).

3.4 | Treatment-emergent sexual dysfunction during antipsychotic drug treatment

A number of studies have employed the ASEX scale to determine the incidence of treatment emergent sexual dysfunction during antipsychotic drug treatment (Atmaca, Kuloglu, & Tezcan, 2005; Byerly et al., 2004; Byerly, Nakonezny, & Rush, 2008; Hanssens et al., 2008; Kalkavoura et al., 2013; Konarzewska et al., 2009; Nakonezny,
An early small case series ($n = 8$) involving a switch to quetiapine in patients with sexual dysfunction associated with previous antipsychotic treatment found a clinically and statistically significant improvement in ASEX total score, significantly decreased total score on the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), and decreased plasma prolactin levels after transition to quetiapine (Byerly et al., 2004). A subsequent study in patients with schizophrenia ($n = 36$), found a statistically significant increase in mean ASEX score after 4 weeks of treatment with quetiapine, compared with scores at baseline: the most frequent dysfunction was diminished sexual desire, both in men (31.8%) and women (28.6%), but there was no significant correlation between ASEX scores and plasma prolactin levels (Atmaca et al., 2005). A cross-sectional survey in symptom-remitted male and female patients with schizophrenia receiving antipsychotic medication ($n = 827$) found that 52.6% had ASEX-determined dysfunction (54.2% reported low sexual desire and 41.7% reported problems in orgasm). In men, erectile dysfunction and ejaculatory problems were seen in 48.1% and 64.2% respectively, and amenorrhea was seen in 24.9% of women. ASEX scores were affected significantly and independently by disease severity in men; ASEX scores were higher in cigarette smokers; low sexual desire was more prevalent among women prescribed first-generation drugs; men undergoing second generation antipsychotic monotherapy had lower ASEX scores than men undergoing combination treatment; and men undergoing combination therapy had more ejaculation problems (Uçok et al., 2007).

A small ($n = 22$) randomized comparator-controlled investigation of the relationship between prolactin and sexual function in outpatients undergoing treatment with risperidone or quetiapine found that higher serum prolactin levels were related to greater ASEX-determined sexual dysfunction in men treated with risperidone, but not with quetiapine (Nakonezny et al., 2007). A small ($n = 42$) randomized double-blind study of either continued risperidone or switch to quetiapine in patients with risperidone-associated sexual dysfunction found no significant treatment effect for either ASEX total score or ASEX items, and no significant treatment x time interaction for either ASEX total scores or ASEX items (Byerly et al., 2008). A large ($n = 555$) comparative investigation in patients with schizophrenia found a significantly greater improvement from baseline in ASEX score with aripiprazole than with comparator drugs: in addition, although serum prolactin levels were similar in the treatment groups at baseline, mean decreases in serum prolactin were 34.2 mg/dL with aripiprazole, compared with 13.3 mg/dL with comparators (Hanssens et al., 2008).

### TABLE 4  ASEX-determined sexual dysfunction during antipsychotic drug treatment

| Study              | N   | Condition                  | Pharmacological treatment               | Results                                                                 |
|--------------------|-----|----------------------------|-----------------------------------------|-------------------------------------------------------------------------|
| Byerly et al. 2004 | 8   | Schizophrenia              | Quetiapine                              | Decreased plasma prolactin levels and improved ASEX-scores after transition to quetiapine, in patients with schizophrenia. |
| Atmaca et al. 2005 | 36  | Schizophrenia              | Quetiapine                              | Significant increase in mean ASEX score after four weeks of treatment with quetiapine compared with scores at baseline. |
| Nakonezny et al. 2007 | 22 M | Schizophrenia, schizoaffective | Quetiapine, risperidone                   | Higher serum prolactin level related to greater ASEX-determined sexual dysfunction in patients treated with risperidone (but not with quetiapine) in patients with schizophrenia and schizoaffective disorders. |
| Byerly et al. 2008 | 22 M 20 F | Schizophrenia             | Quetiapine, risperidone                  | No significant difference in ASEX-scores when switching to quetiapine, compared to risperidone continuation, in patients with schizophrenia. |
| Hanssens et al. 2008 | 332 M 223 F | Schizophrenia             | Aripiprazole                             | Significantly greater improvement from baseline in ASEX score with aripiprazole than with comparator drugs, in patients with schizophrenia. |
| Konarzewska et al. 2009 | 89 M | Schizophrenia             | Risperidone, olanzapine                  | ASEX scores were significantly higher in patients on risperidone, compared to patients on olanzapine, in patients with schizophrenia. |
| Uçok et al. 2007 | 827 | Schizophrenia              | Various antipsychotics                   | 52.6% of patients with schizophrenia in remission who received antipsychotics has ASEX-determined dysfunction. |
| Kalkavoura et al. 2013 | 80  | Schizophrenia              | Various antipsychotics                   | Improved ASEX-scores on augmentation with cabergoline in patients with schizophrenia receiving antipsychotics. |
| Nunes et al. 2013 | 50  | Schizophrenia              | Lodenafil                                | No difference between augmentation with lodenafil and placebo in antipsychotic-treated schizophrenia patients with erectile dysfunction. |
A study in male patients with schizophrenia undergoing antipsychotic drug treatment (n = 89) found that ASEX scores were significantly higher in patients on risperidone, compared to patients on olanzapine: sexual dysfunction and treatment non-adherence were not related to either prolactin or gonadal hormone levels (Konarzewska et al., 2009). An investigation of augmentation with cabergoline in patients (n = 80) receiving a range of antipsychotics found a reduction in prolactin levels with cabergoline treatment in all patients, with mean levels of 73.3 ng/mL (±46.8) to 42.0 ng/mL (±27.8) at month 3 and 27.1 ng/mL (±20.4) at month 6: mean total ASEX scores also declined, from 19.1 (±5.1) to 17.6 (±5.5) at month 3, and 15.0 (±6.5) at month 6 (Kalkavoura et al., 2013). Finally, a randomized, double-blind, crossover, placebo-controlled investigation of lodenafil in male patients (n = 50) with schizophrenia and erectile dysfunction found that both lodenafil and placebo were associated with an improvement in ASEX, IIEF scale, PANSS, and QLS scores, with no statistical differences between treatment groups in all sexual domains or in hormone levels (Nunes et al., 2013).

### 3.5 Primary sexual dysfunction

The ASEX has been used to study primary sexual dysfunction and the potential benefit of pharmacological agents to modulate sexual drive and function (Table 5). A study involving military personnel (n = 367) found 8.45% ASEX-reported dysfunction. This was correlated with erectile dysfunction in 33.24% measured by the IIEF. Risk factors identified by the study were age 21–40 years, and poor physical and psychosocial health (Wilcox et al., 2014).

Male patients with congenital hypogonadotrophic hypogonadism (n = 39) had significantly higher scores for BDI, BAI, and ASEX than controls (n = 40) at baseline. ASEX and BDI scores significantly improved after testosterone treatment, while the improvement in the BAI score was not statistically significant. Treatment-naive hypogonadal patients had more severe symptoms of sexual dysfunction, anxiety, depression, and worse quality of life. Six months of testosterone treatment was associated with improvement in all parameters, suggesting that low endogenous levels of testosterone might be related to the increased prevalence of psychological symptoms at baseline (Aydogan et al., 2012).

A randomized controlled trial, studying placebo and nocebo responses in heterosexual men (n = 48), found increased levels of sexual function after administration of cabergoline with significant effects for several parameters measured by ASEX, and the Acute Sexual Experience Scale (ASES) (Krüger et al., 2003). Placebo effects were induced only to a small degree. No negative effects on sexual parameters in the nocebo condition were noted. This paradigm could induce only small placebo and nocebo effects (Kruger et al., 2016). Intranasal oxytocin administration to healthy participants (n = 58), did not alter “classical” parameters of sexual function, such as sexual drive, arousal or penile erection and lubrication. However, analysis of variance and a hierarchical linear model found that oxytocin increased the intensity of orgasm and contentment after sexual intercourse, these effects being more pronounced in men. Men additionally indicated higher levels of sexual satiety after sexual intercourse with oxytocin administration. Women felt more relaxed and subgroups indicated better abilities to share sexual desires or to empathize with their partners (Behnia et al., 2014).

### Table 5 ASEX rated primary sexual dysfunction and treatment response

| Study                  | N     | Condition                        | Pharmacological treatment | Results                                                                 |
|------------------------|-------|----------------------------------|---------------------------|-------------------------------------------------------------------------|
| Behnia et al. 2014     | 58    | Healthy heterosexual volunteers  | Oxytocin                  | Intransal oxytocin administration exerted differential effects on parameters of sexual function and partner interactions |
| Wilcox, Redmond, and Hassan, 2014 | 367   | Healthy volunteers               |                           | ASEX-reported dysfunction 8.45% in military personnel.                   |
| Kruger et al. 2016     | 48 M  | Healthy volunteers               | Cabergoline               | Significant improvement of ASEX and ASES with cabergoline, healthy men. |
| Vaillancourt-Morel et al. 2017 | 875   | Cyberpronography users           |                           | Less ASEX-satisfaction associated with higher dysfunction in compulsive pornography users. |
| Chudakov, Ben Zion, and Belmaker, 2007 | 10 F  | Hypoactive sexual desire disorder | Testosterone gel versus placebo | Significant improvement in the ASEX arousal item with testosterone gel, in fs with hypoactive sexual desire disorder. |
| Aydogan et al. 2012    | 39 M  | Congenital hypogonadotropic hypogonadism | Testosterone replacement treatment | Improvement of ASEX, BDI and BAI with testosterone replacement in patients with congenital hypogonadotropic hypogonadism. |
A randomized double-blind crossover in women with “hypoactive sexual desire disorder” (n = 10), found significantly improved ASEX-item 2 (arousal) scores on testosterone gel, compared to placebo: similar trends were found in Sexual Function Questionnaire (SFQ-V1) (Quirk et al., 2002) scores (Chudakov et al., 2007).

A cluster-analytic study of use of pornography (n = 875), found that recreational users reported higher ASEX-satisfaction and lower sexual compulsivity, avoidance, and dysfunction, whereas users with a compulsive profile presented lower ASEX satisfaction and dysfunction and higher sexual compulsivity and avoidance. Highly distressed less active users were sexually less satisfied and reported less sexual compulsivity and more sexual dysfunction and avoidance. A larger proportion of women and of dyadic users was found among recreational users, whereas solitary users were more likely to be in the highly distressed less active profile, and men were more likely to be in the compulsive profile (Vaillancourt-Morel et al., 2017).

### 3.6 Sexual dysfunction with non-psychotropic medications

Few studies have used the ASEX to determine potential dysfunction associated with non-psychotropic medication (Table 6). A study in patients receiving finasteride (n = 79) utilized an “ad hoc questionnaire” of 100 questions (elaborated by the study authors) (Di Loreto et al., 2014); and ASEX at the time of enrolment and retrospectively before finasteride use. ASEX found that 40.5% of participants had difficulties achieving and maintaining erection, and 3.8% had never achieved erection. Achieving orgasm was difficult in 16.5%, and never achieved by 2.5%. By the ad hoc questionnaire, the most frequent sexual symptoms referred were loss of penis sensitivity (87.3%), decreased ejaculatory force (82.3%), and low penile temperature (78.5%). The most frequent non-sexual symptoms were reduced feeling of life pleasure or emotions (anhedonia) (75.9%); lack of mental concentration (72.2%), and loss of muscle tone/mass (51.9%) (Chiriaco et al., 2016). Healthy young men without any baseline sexual dysfunction (n = 54), who were taking finasteride for male pattern hair loss, had ASEX-reported sexual side effects associated with finasteride (89%), after 9–16 months (mean 14 months). Neither the length of finasteride use nor the duration of the sexual side effects correlated to changes in scores of sexual dysfunction. Persistent sexual side effects (≥3 months) continued for many months or years despite the discontinuation of finasteride (Inwig, 2012). Another study in women with overactive bladder (n = 30) found that tolterodine immediate release improved mean total ASEX scores compared to baseline: mean item scores for sexual desire, arousal, vaginal lubrication, orgasm, and orgasm satisfaction all improved significantly at follow-up (Hajebrahimi et al., 2008).

### Table 6 ASEX rated non-psychotropic treatment emergent sexual dysfunction

| Study                                      | N   | Condition                                 | Pharmacological treatment | Results                                                                 |
|--------------------------------------------|-----|-------------------------------------------|----------------------------|------------------------------------------------------------------------|
| Hijabrahimi, Azaripour, & Sadeghi-Bazargani, 2008 | 30 F | Overactive bladder Tolterodine            | Tolterodine improved total ASEX in fs with overactive bladder syndrome. |
| Inwig, 2012                                | 45 M | Male pattern hair loss                    | Finasteride                | 89% sexual dysfunction of healthy patients who received finasteride for M pattern hair loss. |
| Chiriaco, Cauci, Mazzon, & Trombetta, 2016  | 79 M | Alopecia                                  | Finasteride                | 48.3% of patients with alopecia had erectile dysfunction. 19% had problems with orgasm. |

4 | DISCUSSION

DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) introduced some changes to the classification of sexual dysfunctions: including the merger of sexual desire and sexual arousal (American Psychiatric Association, 2013), based on recommendations which suggested that distinction between the two was artificial (Graham, 2010); and the rejection of a linear model for arousal (Graham, Sanders, Milhausen, & McBride, 2004; Janssen, McBride, Yarber, Hill, & Butler, 2008). The five items of the ASEX, however, distinguish between sexual drive and sexual arousal.

The recent criteria, by DSM-5, for the diagnosis of sexual dysfunction requires the presence of clinically significant distress along with sexual difficulties. It is to be mindful that findings from some of the studies included in this review used the term “sexual dysfunction” broadly and not in accordance or predated, the up-to-date definition of the clinical phenomena (according to DSM-5). Therefore, some of the studies included give evidence for the presence of sexual difficulties.

The ASEX scale appears to have excellent internal consistency and scale reliability and strong test–retest reliability: furthermore, ASEX scores appear to correlate well with factors and related items on other validated questionnaires for assessing sexual dysfunction. ASEX has very high sensitivity and specificity, and very high positive and negative predictive values. ASEX is available in 43 languages. Studies which have examined the psychometric properties of the Turkish, Thai, Chinese, and Arabic versions of ASEX found the translated versions to have psychometric properties comparable to those of the original English version.

Validation studies have utilized cohorts with various psychiatric disorders, schizophrenia, schizoaffective disorder, and end-stage renal failure. The ASEX was found to have satisfactory validity and reliability in studies of sexual dysfunction in specific patient groups: primary sexual dysfunction, specific psychiatric disorders, and specific physical
illnesses. The psychometric properties of ASEX in cohorts with anxiety disorders were largely uncertain, and little is known about possible relationships between peripheral biological markers and ASEX scores.

Most studies have found higher rates (48–58.4%) of ASEX-reported sexual dysfunction in patients with substance misuse when compared with controls. Patients with MDD were found to have elevated rates of sexual dysfunction (73.4% in mixed samples), and ASEX-reported dysfunction was found to correlate positively with the presence and severity of affective symptoms in patients with MDD. A small group of studies have found no significant correlation between ASEX scores and plasma prolactin levels with quetiapine or aripiprazole in patients with schizophrenia.

Many studies have employed the ASEX to investigate treatment-emergent sexual dysfunction, principally with antidepressant and antipsychotic drugs. Between 32 and 73% of patients receiving antidepressant and antipsychotic treatment were found to have sexual dysfunction. Studies which compared groups based on response to treatment found sexual dysfunction in 49.6% in treatment non-responders and 33.2% in treatment responders, with an improvement percentage (IP) –1.6% on ASEX total score in treatment responders. Acute treatment with paroxetine was found to have higher rates of sexual dysfunction (62.8%). Head-to-head comparative studies have generally found no inferiority between different antidepressants in the sexual dysfunction domain. Studies have found beneficial effects for aripiprazole augmentation, for switching to agomelatine, and for switching to mirtazapine. 52.6% of patients receiving antipsychotics were found to have sexual dysfunction, and a significantly higher ASEX total score was seen in patients receiving risperidone, compared to patients receiving olanzapine, quetiapine or aripiprazole. Augmentation with cabergoline was associated with improved ASEX scores in patients undergoing antipsychotic treatment.

Studies have found sexual dysfunction in 47–69.4% in patients with renal disease, dysfunction being more pronounced in patients receiving peritoneal dialysis, when compared to those receiving haemodialysis. Studies in patients with malignant conditions have found a significant increase in ASEX scores when compared with controls, post-diagnosis and after cancer treatment. Patients with a number of skin conditions (hidradenitis, genital warts, psoriasis, vitiligo, and neurodermatitis) were found to have a higher incidence of sexual dysfunction when compared with controls, and patients with some movement disorders (parkinsonism, multiple sclerosis) had sexual dysfunction more frequently than controls.

Little is known about the utility of ASEX in anxiety disorders and psychogenic sexual dysfunction. Future research should also look into the utility of ASEX for patients undergoing psychological interventions and couple therapies. Future studies should also include investigation of response shift.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interests.

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