

## ORIGINAL PAPER

**Sexual Dysfunction Related to Non-SSRI Second Generation Antidepressants: A Meta-Analysis***Yee A, Kanagasundram S, Gill JS, Zainal NZ*

Department of Psychological Medicine, Psychological Medicine Research Group of University Malaya (PARADIGM), Faculty of Medicine, University Malaya, 50603 Kuala Lumpur, Malaysia

**Abstract**

**Objective:** This systematic review is aimed to quantitatively summarise the prevalence of sexual dysfunction among non-SSRI second generation antidepressants namely agomelatine, bupropion, duloxetine, venlafaxine, and mirtazapine. **Methods:** Relevant studies published from inception till December 2012 were identified by searching PubMed, OVID and Embase. We included all literatures encompassing randomized controlled, cohort, case-controlled and cross-sectional studies, which contained quantitative data for prevalence on all aspects of sexual dysfunction in depressive patients who were older than 18 years of age. Heterogeneity, publication bias and odds ratio were assessed thoroughly. **Results:** In the non-SSRI second generation antidepressant group which consisted of 17,316 subjects, various studies showed the range of sexual dysfunction prevalence between 0% and 67%. Sexual dysfunction in patients who took non-SSRI second generation antidepressants constituted a meta-analytical pooled prevalence of 15%, and 36% in those who took SSRIs. The combined relative risk of sexual dysfunction in the non-SSRI second generation antidepressant group when compared with SSRI was 0.57. **Conclusions:** The pooled prevalence of sexual dysfunction in non-SSRI second generation antidepressant is lower than in SSRI antidepressants.

**Keywords:** Sexual Dysfunction, Non-SSRI, Antidepressants

**Introduction**

Antidepressant medications are currently one of the most prescribed class of drugs<sup>1, 2</sup>. This can be explained to a certain extent by the fact that the current generation of antidepressants are relatively well tolerated and safe. Furthermore the indications for many antidepressants are varied, going far

beyond just for depression itself. Unfortunately, sexual dysfunction is a common, well-known adverse effect of antidepressants, even among the newer generations<sup>3-6</sup>. The prevalence of sexual dysfunction among the general population of adult men is 20-30% and adult women 40-45% and the use of antidepressant increases this value.<sup>7</sup> These adverse effects may lead

to poor compliance with medication, and lead to loss of self esteem and distress, which may worsen the primary disorder that we are trying to treat. Almost every facet in the spectrum of sexual dysfunction can be associated with antidepressant use, including loss of desire and arousal, orgasmic difficulties (anorgasmia, delayed orgasm, hyperorgasmia), painful orgasm, erectile dysfunction, priapism, dyspareunia and vaginismus.

The role of antidepressants in the etiology of sexual dysfunction first gained considerable interest with the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the late 80s and evidence from controlled studies and review papers have gained in abundance ever since then<sup>8</sup>. However, antidepressants have continued to evolve ever since, and we now have several different classes of antidepressants since then, namely the serotonin noradrenaline reuptake inhibitors (SNRIs) such as Venlafaxine and Duloxetine, noradrenaline dopamine reuptake inhibitors (NDRIs) such as Bupropion, noradrenergic and specific serotonergic antidepressants (NaSSA) such as Mirtazapine, and melatonergic antidepressants such as Agomelatine. Unfortunately, even these non-SSRI second generation antidepressants have been associated with sexual dysfunction. However unlike their earlier predecessors, such as the SSRIs, comprehensive reviews on sexual dysfunction among these non-SSRI antidepressants are lacking. Realizing this, we aimed to quantitatively summarise the prevalence of sexual dysfunction among

these non-SSRI second generation antidepressants namely agomelatine, bupropion, duloxetine, venlafaxine, and mirtazapine. The second objective was to determine the risk of sexual dysfunction emerged in these antidepressants when compared to SSRI.

## **Methods**

### *Search strategy and selection criteria*

AY and SK developed the tools to extract the data and review protocol, with strict adherence to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A thorough search was performed of all literature in English published in PubMed, OVID and EMBASE databases, from inception to December 2012, using the search terms found in Box 1. All randomized controlled studies, cohort, case-control, and cross-sectional studies, that presented with original quantitative data for prevalence on all aspects of sexual dysfunction in depressed patients aged 18 years and above at diagnosis were included. All methods of diagnosing sexual dysfunction among Major Depressive Disorder patients were accepted. Case reports, case series, systemic reviews, and all duplicate publications, which have two or more studies looking at the same sample, were excluded. We also excluded studies, which included patients who were on treatment for sexual dysfunction using antidepressants.

**Box 1.** Search strategies (conducted January 2013)

PubMed: (Sexual dysfunction [sh] OR Sexual dysfunctions [sh] OR Sex disorder [sh] OR Sex disorders [sh] OR Sexual disorder [sh] OR Sexual disorders [sh] OR Sexual function [sh] OR Sexual performance [sh] OR Physiological Sexual Dysfunction [sh] OR Physiological Sexual Dysfunctions [sh] OR Physiological Sexual Disorder [sh] OR Physiological Sexual Disorders [sh] OR Psychological Sexual Dysfunction [sh] OR Psychological Sexual Dysfunctions [sh] OR Sexual Aversion Disorder [sh] OR Sexual Aversion Disorders [sh] OR Desire disorder [sh] OR Orgasmic Disorder [sh] OR Orgasmic Disorders [sh] OR Sexual Arousal Disorder [sh] OR Sexual Arousal Disorders [sh] OR Hypoactive Sexual Desire Disorder [sh] OR Hypoactive disorder [sh] OR Erectile dysfunction [sh] OR Premature ejaculation [sh] OR Delayed ejaculation [sh] OR Impotence [sh] OR Decreased libido [sh] OR Infertility [sh] OR Vaginismus [sh] OR Dyspareunia [sh]) AND (Duloxetine [sh] OR Cymbalta [sh] OR Valdoxan [sh] OR Agomelatin [sh] OR Remeron [sh] OR Mirtazapine [sh] OR Efexor [sh] OR Effexor [sh] OR Venlafaxine [sh] OR Bupropion [sh]) AND (Male [sh] OR Males [sh] OR Female [sh] OR Females [sh] OR Man [sh] OR Men [sh] OR Woman [sh] OR Women [sh])

OVID: (Sexual dysfunction [sh] OR Sexual dysfunctions [sh] OR Sex disorder [sh] OR Sex disorders [sh] OR Sexual disorder [sh] OR Sexual disorders [sh] OR Sexual function [sh] OR Sexual performance [sh] OR Physiological Sexual Dysfunction [sh] OR Physiological Sexual Dysfunctions [sh] OR Physiological Sexual Disorder [sh] OR Physiological Sexual Disorders [sh] OR Psychological Sexual Dysfunction [sh] OR Psychological Sexual Dysfunctions [sh] OR Sexual Aversion Disorder [sh] OR Sexual Aversion Disorders [sh] OR Desire disorder [sh] OR Orgasmic Disorder [sh] OR Orgasmic Disorders [sh] OR Sexual Arousal Disorder [sh] OR Sexual Arousal Disorders [sh] OR Hypoactive Sexual Desire Disorder [sh] OR Hypoactive disorder [sh] OR Erectile dysfunction [sh] OR Premature ejaculation [sh] OR Delayed ejaculation [sh] OR Impotence [sh] OR Decreased libido [sh] OR Infertility [sh] OR Vaginismus [sh] OR Dyspareunia [sh]) AND (Duloxetine [sh] OR Cymbalta [sh] OR Valdoxan [sh] OR Agomelatin [sh] OR Remeron [sh] OR Mirtazapine [sh] OR Efexor [sh] OR Effexor [sh] OR Venlafaxine [sh] OR Bupropion [sh]) AND (Male [sh] OR Males [sh] OR Female [sh] OR Females [sh] OR Man [sh] OR Men [sh] OR Woman [sh] OR Women [sh])

EMBASE: (Sexual dysfunction [sh] OR Sexual dysfunctions [sh] OR Sex disorder [sh] OR Sex disorders [sh] OR Sexual disorder [sh] OR Sexual disorders [sh] OR Sexual function [sh] OR Sexual performance [sh] OR Physiological Sexual Dysfunction [sh] OR Physiological Sexual Dysfunctions [sh] OR Physiological Sexual Disorder [sh] OR Physiological Sexual Disorders [sh] OR Psychological Sexual Dysfunction [sh] OR Psychological Sexual Dysfunctions [sh] OR Sexual Aversion Disorder [sh] OR Sexual Aversion Disorders [sh] OR Desire disorder [sh] OR Orgasmic Disorder [sh] OR Orgasmic Disorders [sh] OR Sexual Arousal Disorder [sh] OR Sexual Arousal Disorders [sh] OR Hypoactive Sexual Desire Disorder [sh] OR Hypoactive disorder [sh] OR Erectile dysfunction [sh] OR Premature ejaculation [sh] OR Delayed ejaculation [sh] OR Impotence [sh] OR Decreased libido [sh] OR Infertility [sh] OR Vaginismus [sh] OR Dyspareunia [sh]) AND (Duloxetine [sh] OR Cymbalta [sh] OR Valdoxan [sh] OR Agomelatin [sh] OR Remeron [sh] OR Mirtazapine [sh] OR Efexor [sh] OR Effexor [sh] OR Venlafaxine [sh] OR Bupropion [sh]) AND (Male [sh] OR Males [sh] OR Female [sh] OR Females [sh] OR Man [sh] OR Men [sh] OR Woman [sh] OR Women [sh])

### ***Data extraction and classification***

AY and SK extracted the primary data independently, which was then reviewed systemically. Firstly, the sampling method was assessed for each study. Secondly, a four-point quality rating and a five-point bias-rating score was applied to each study. Quality-rating score was used to assess the study sample size, design, attrition criterion method and method of dealing with possible confounders with the following scale: 1=low quality; 2= low-to-medium quality; 3=medium-to-high quality; and 4= high quality. Thirdly, a five-point bias-rating score was applied to each study. Bias-rating score was used to assess possible bias in assessment of age, clinical setting, and outcomes with the following score: 0=no appreciable bias risk; 1= low bias risk; 2= low-to-medium bias risk; 3=medium-to-high bias risk; and 4-high bias risk (Mitchell et al., 2011). Any area of disagreement was resolved by JG and NZ.

### ***Statistical analysis***

We pooled individual study data with DerSimonian-Laird meta-analysis. Heterogeneity was invariably moderate to high; therefore, a random effects meta-analysis was done with StatsDirect (version

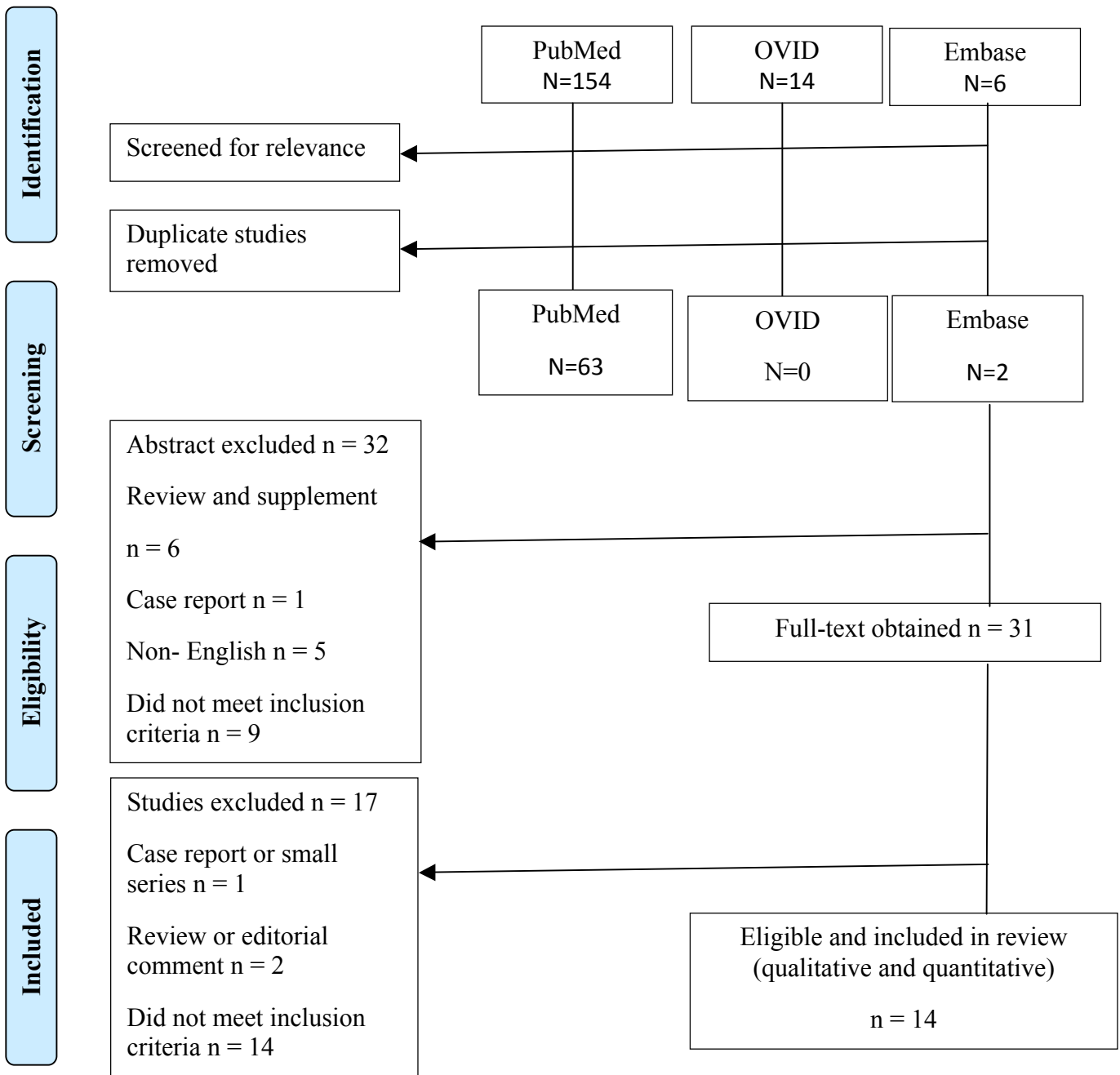
2.7.9). We used the  $I^2$  test to assess heterogeneity (threshold were  $\geq 80\%$ =moderate and  $\geq 90\%$ =high), and also assessed publication bias with Begg-Mazumdar and Egger tests. For comparative and sub analyses we needed a minimum of three independent studies to justify analysis according to convention. Relative risk was calculated only for randomized controlled studies that compared the non-SSRI second generation antidepressants and SSRI through a fixed effect s meta-analysis.

## **Results**

### ***Selection of studies***

The initial search strategy identified 174 titles: 154 from Pubmed, 14 from Ovid and 6 from EMBASE (Figure 1). After title screening and elimination of duplicate publications, 65 publications remained: 63 from Pubmed and 2 from EMBASE. We then excluded 32 publications after reviewing the abstract. The full text of the remaining 31 (not including the duplicates) studies were reviewed, of which 14 eligible studies were included in this review. Data extraction is shown in figure 1 in accordance with Quality of Reporting of Meta-analyses guidelines.

**Figure 1.** PRISMA Flow Diagram



Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine*. 2009 Aug 18;151(4):264-9.

***Description of selected study populations***

The designs and aims of all the eligible studies were listed in Table 1. Most of articles were prospective in nature and centered on sexual dysfunction as the outcome measure. Majority of them were conducted at outpatient clinics. Five studies had comparative groups while the majority did not. Seven of the studies were conducted in the USA while five studies were from Europe (the UK, Greece, Spain, and France). Canada contributed three studies while Korea, Taiwan and Argentina contributed one study. The mean age at the study entry

was  $42.5 \pm 5.9$ . There were 125365 subjects in the studies (Table 2).

***Sampling method, methodological quality and bias assessment***

Six of the studies used consecutive or random sample, while others either used non randomized sampling or just did not report the sampling method used. Six studies scored 4 in quality assessment but just two score 0 in bias risk assessment (Table 1). Of these only five studies were randomized controlled studies<sup>9-13</sup>.

**Table 1.** The methodology and sexual dysfunction-related research question in 14 eligible studies.

First author	Sampling method <sup>a</sup>	Quality <sup>b</sup>	Bias risk <sup>c</sup>	Design <sup>c</sup>	Setting	Criteria for definition of sexual dysfunction	Criteria for definition of depression	Control Group	Country Population source
Anderson, 2012	NR	2	2	RS	NR	ICD-9-CM	ICD-9-CM diagnostic code of 296.2 or 296.3	No	USA
Boyarsky, 1999	1	2	3	PS	Outpatient	ASEX	DSM-IV criteria; HAM- D	No	USA
Clayton, 2002	0	2	2	CS	Outpatient	CSFQ-14	NR	No	USA
Clayton, 2007	0	4	2	RCT	Outpatient	CSFQ	DSM-IV; M.I.N.I.	Placebo	USA
Delgado, 2005	0	4	0	RCT	NR	ASEX	DSM-IV criteria; HAM- D	Placebo	USA
Koutouvidis, 1999	NR	1	3	PS	Outpatient	NR	ICD; HDRS- 17	No	Greece
Kennedy, 2008	0	4	1	RCT	Outpatient	Sex FX	MADRS; CGI-S; CGI	Venlafaxine	Canada
Lee, 2010	1	2	3	CS	Outpatient	ASEX	DSM-IV; BDI	No	Korea
Lin, 2011	NR	2	NR	PS	Outpatient	ASEX-CV	DSM-IV-TR criteria; DSSS; HDRS; HADS	No	Taiwan

Mackay, 1999	NR	2	2	PS	Outpatient	Clinical interview	NR	No	UK
Montejo, 2001	1	3	1	PS	Outpatient	PRSexDQ	DSM-IV	No	Spain
Olié, 2010	0	3	2	RCT	Outpatient	Self report	DSM-IV-TR; M.I.N.I.; MADRS	Milnapricin	France
Segraves, 2000	0	4	0	RCT	Outpatient	DSM-IV; Clinical interview	Clinical interview	sertraline	USA
Sapetti, 2012	NR	2	2	PS	NR	ASEX; IIEF; VAS	DSM-IV; MADRS	No	Argentina

---

<sup>a</sup>Sampling method: 0= consecutive or random sample, 1= non random sampling, <sup>b</sup>Quality: 1=low quality, 2=low-to-medium quality, 3=medium-to-high quality, 4=high quality. <sup>c</sup>Bias risk: 0=no appreciable bias risk, 1=low bias risk, 2=low-to-medium bias risk, 3=medium-to-high bias risk, and 4=high bias risk. ASEX=Arizona Sexual Experiences Scale. ASEX-CV=Arizona Sexual Experience Scale-Chinese Version. BDI=Beck Depression Inventory. CS= Cross sectional. CGI=Clinical Global Improvement Scale. CGI-S=Clinical Global Impression Severity of Illness Scale. CSFQ=Changes in Sexual Functioning Questionnaire. CSFQ-14=Changes in Sexual Functioning Questionnaire. DSSS=Depression and Somatic Symptoms Scale. DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition. DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition, Text revision. HAM-D=Hamilton Depression Rating Scale. HADS=Hospital Anxiety and Depression Scale (HADS). HDRS-17=Hamilton Depression Rating Scale-17. ICD-9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification. IIEF=International Index of Erectile Function. MADRS=Montgomery-Asberg Depression Rating Scale. M.I.N.I.=Mini International Neuropsychiatric Interview. PRSexDQ=The Psychotropic-Related Sexual Dysfunction Questionnaire. PS= Prospective Study. RCT=Randomized control trial. RS= Retrospective Study. Sex FX= Sex Effects Scale. UK=United Kingdom. USA=United States of America. VAS=Visual Analogue Scale. NR=Not reported.



***Data collection in selected studies***

Table 2 depicts the various methods used to elicit data and the defining criteria used for sexual dysfunction. Of these 8 studies identified sexual dysfunction in the patients using self-administered questionnaires (ASEX, SFQ, CSFQ, ASEX-CV, IIEF, VAS)<sup>14-19</sup>, 3 studies used diagnostic interviews like (ICD-9-CM, DSM-IV, PRSexDQ)<sup>9, 20, 21</sup> and other self-reporting methods. A majority of the studies did not have well defined criteria for sexual dysfunction. A variety of questionnaires were used to assess sexual dysfunction in the sampled population. These questionnaires contained either a single question<sup>22</sup> or a series of questions on sexual dysfunction from which a total sum score was calculated<sup>10, 23-26</sup>. The minimal time period for each of the subjects in this study was at least 6 weeks (Table 2).

**Table 2.** Description of the populations in the 14 included studies.

First Author	Number in analytic sample			Antidepressant, Mean age at study entry, year	Method	Time period (weeks)	Definition of sexual dysfunction	Prevalence rate (%) of sexual dysfunction			
	Total	Male	Female					N <sup>#</sup> /total number (%)			
Boyarsky, 1999	18	6	12	M= 21-64	SAQ	12	ASEX : Total score of ≥19, any one item with an individual score ≥5 , or any three items with individual scores ≥4	M=2/18 (11.1%)			
Mackay, 1999	74748				I	24	Clinician reported one question regarding impotence or ejaculation failure in male patients	<u>Impotence/ejaculation failure</u>			
	F=12962	F=3690	F=8863	F=49.75				F =3 / 3690 (1.0)			
	S=12734	S=3910	S=8729	S=48.65				S=13/ 3910 (3.1)			
	P=13741	P=4373	P=9279	P=48.7				P=54/ 4373 (11.1)			
	V=12642	V=4349	V=8214	V=47.6				V=30/ 4349 (5.8)			
Koutouvidis, 1999	11	6	5	M=30.5	SAQ	6	NR	0/11 (0%)			
Segraves, 2000	241			BSR=39	I	16	DSM-IV definitions for sexual dysfunction disorders	<u>Overall Sexual dysfunction</u>			
	BSR=119	BSR=67	BSR=52	S=40				Total	Male	Female	
	S =122	S =65	S =57					BSR=	14/119	10/62 (15)	4/57 (7)
									(11.7)		

S = 65/122 41/64 (63) 24/58  
(53) (41)

Montejo, 2001	1022	412	610	F,S,FV,P,C,V,M <u>Overall mean age</u> 39.8	I	NR	Psychotropic- Related Sexual Dysfunction Questionnaire-7 items.	Overall =604/1022(59.1) F=161/279 (57.7) S=100/159 (62.9) FV=48/77 (62.3) P=147/208 (70.7) C=48/66 (72.7) V=37/55 (67.3) M=12/49 (24.4)	
Clayton, 2002	6297	1763	4534	BIR,BSR,C,F,M, P,S,V,VXR  Overall Mean age NR	SAQ	NR	CSFQ: Total score ≤ 41 for women and 47 for men	<u>Overall population</u> N=6268 Overall = 2320/6268 (37) BIR= 12/51(22) BSR=146/584(25) C=270/730(37) F=563/1521(37) M=27/64( 41) P=465/1132(41) S=451/1098(41) V= 40/117(35) VXR=258/629(41)	<u>Target population<sup>a</sup></u> N=798 Overall = 1912/798 (24) BIR =4/45(7) C=25/83(30) F = 62/245(25) P=45/159(28) S=45/161(28) VXR=21/70(30)

MJP Online Early

MJP-01-10-15

Delgado, 2005	870			D,P, PLB <u>Overall mean age</u> 40.5 - 45.2	SAQ	8	ASEX : Total score of $\geq 19$ , any one item with an individual score $\geq 5$ , or any three items with individual scores $\geq 4$	D= 110/241 (46.4) P=66/107 (61.4) PLB = 37/127 (28.8)
Clayton, 2007	547 D =273 E=274			D,E,PLB <u>Overall mean age</u> NR	SAQ	32	CSFQ: Total score $\leq 41$ for women and 47 for men.	D= 17/51 (33.3) E=19/39 (48.7) PLB=4/24 (16.7)
Kennedy, 2008	277 A=137 VXR =140			A, V <u>Overall mean age</u> 40.9	I	12	Sexual function was determined by the 13-item clinician- administered Sex Effects Scale (sex FX).	<u>SA-R<sup>b</sup></u> A= 5/60 (7.3),V= 9/51 (15.7)
Lee, 2010	101 C=20 F =13 P=24 V=22 M =22	46 C=8 F =6 P=12 V=11 M =9	55 C=12 F =7 P=12 V=11 M =13	<u>Overall mean age</u> 42 C=40.5,F=41.4 P=42.6, V=40.6 M=45.6	SAQ	4	ASEX : Total score of $\geq 19$ , any one item with an individual score $\geq 5$ , or any three items with individual scores $\geq 4$	Overall =47 (46.5%) C=12/20 (60), V=12/22 (54.5) P =13/24 (54.2) F=6/13 (46.2) M=4/22 (18.2)
Olié, 2010	134 Mil=60			Mil=44.6 V=42.7	SAQ	24	Self report of adverse effects	Orgasm disorder V =16/91(17)

Author	V	SAQ	SAQ	SAQ	SAQ	SAQ	SAQ	SAQ	SAQ
Lin, 2011	V=74 135 Complete group=70	34	101	V Complete group=28.1	SAQ	4	ASEX : Total score of ≥19, any one item with an individual score ≥5 , or any three items with individual scores ≥4	Mil=0/90 (0%) V=43/70 (61.4)	
Anderson, 2012	40017 67183 SSRI =26,284 SNRI =4975 B=5636 M=969			SSRI=41.18 SNRI=43.21 B=38.89 M=48.8	SAQ	4	Sexual function was determined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD- 9-CM).	SSRI=80/23620 (0.3) SNRI=13/4762 (0.3%) B=12/5095(0.2) M= 1/901 (0.1)	
Sapetti, 2012	28	15	13	A=48	SAQ	12	ASEX; Score=19– 30: IIEF and the VAS for desire, arousal, time and intensity of orgasm, and vaginal lubrication.	A=0/25 (0%)	

#Incidence sexual dysfunction among patients that take antidepressants (N)

<sup>a</sup> subpopulation of patients without other probable causes of sexual dysfunction <sup>b</sup>Sexually Active-Remitters): subjects achieved ≤12 on MADRS.

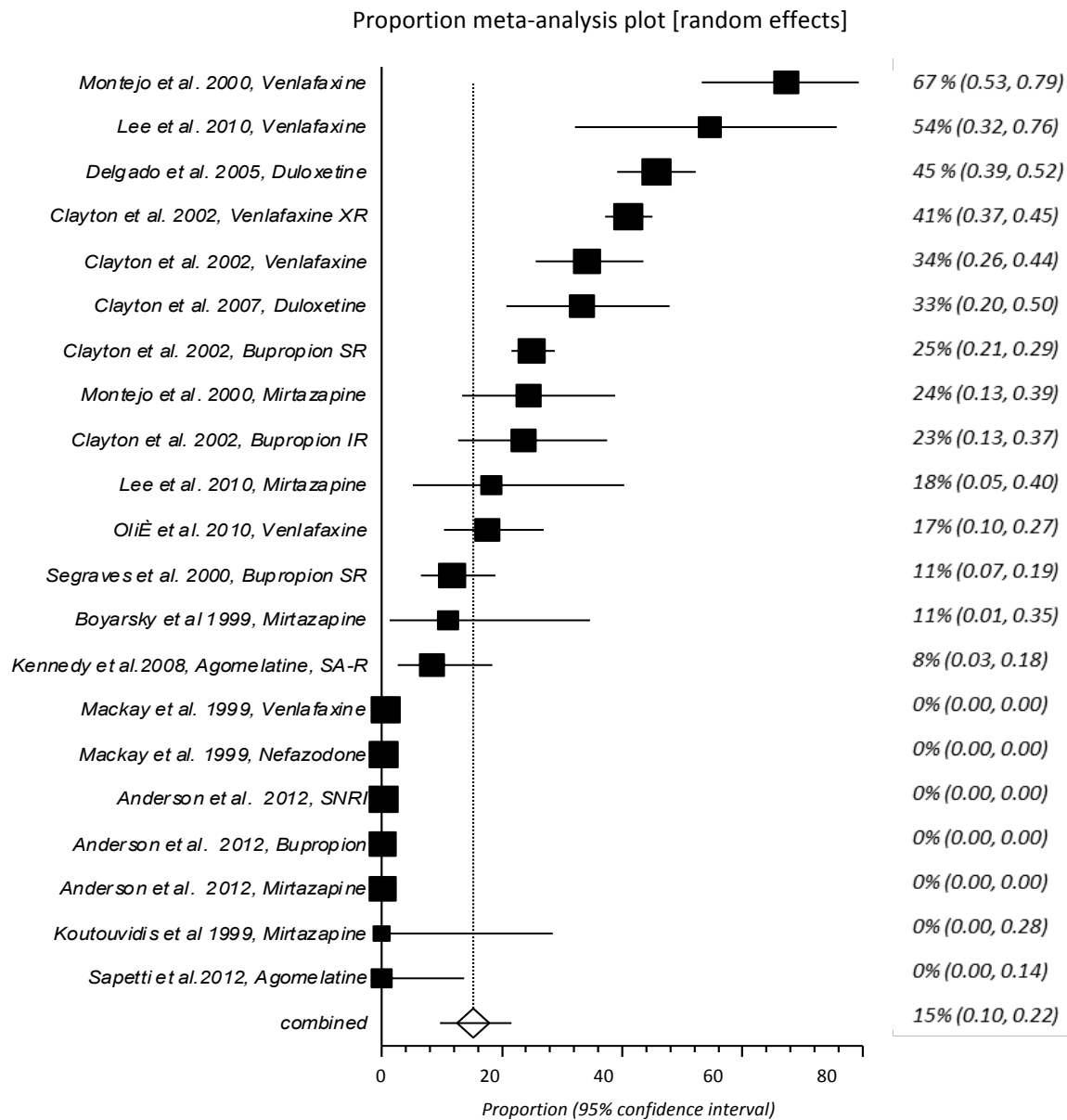
A=Agomelatine. ASEX=Arizona Sexual Experiences Scale. ASEX-CV=Arizona Sexual Experience Scale-Chinese Version. BIR=Bupropion immediate release. BSR=Bupropion sustained release. C=Citalopram. CSFQ=Changes in Sexual Functioning

Questionnaire. CSFQ-14=Changes in Sexual Functioning Questionnaire. D=Duloxetine. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition. DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text revision. F=Fluoxetine. E=Escitalopram. FV= Fluvoxamine. ICD-9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification. I= face to face interview. IIEF=International Index of Erectile Function. IRSD-F=Investigator-Rated Sexual Desire and Functioning Scale. M=Mirtazapine. Mil=Milnaciprin. P=Paroxetine. PLB=Placebo. PRSexDQ=The Psychotropic-Related Sexual Dysfunction Questionnaire. S=Sertraline. SAQ=Self administered Questionnaires. Sex FX= Sex Effects Scale. SNRI= Serotonin-norepinephrine reuptake inhibitors. SSRI=Serotonin Selective Reuptake Inhibitors. V=Venlafaxine. VXR=Venlafaxine extend release. VAS=Visual Analogue Scale.

### ***Prevalence of sexual dysfunction***

Among the non-SSRI second generation antidepressants (Mirtazapine, high dose venlafaxine, duloxetine, bupropion, agomelatine) group<sup>9, 13, 20, 23, 25, 27, 28</sup>, prevalence of sexual dysfunction ranged from 0% to 67% in the individual studies. In other studies the prevalence has even been noted to be higher<sup>29</sup>. There were 17316 subjects. Meta-analytical pooled prevalence of sexual dysfunction among patients who were given non-SSRI second antidepressants was 15% (95% CI 0.11 – 0.25) (Figure 2). In the SSRI (sertraline, fluoxetine, paroxetine, citalopram, low dose venlafaxine, escitalopram) group, there were 41294 subjects, and the prevalence of sexual dysfunction ranged from 0.1% to 72% in individual studies. Meta-analytical pooled prevalence of sexual dysfunction in patients using SSRI was 36% (95% CI 0.25 to 0.48) (Figure 3).

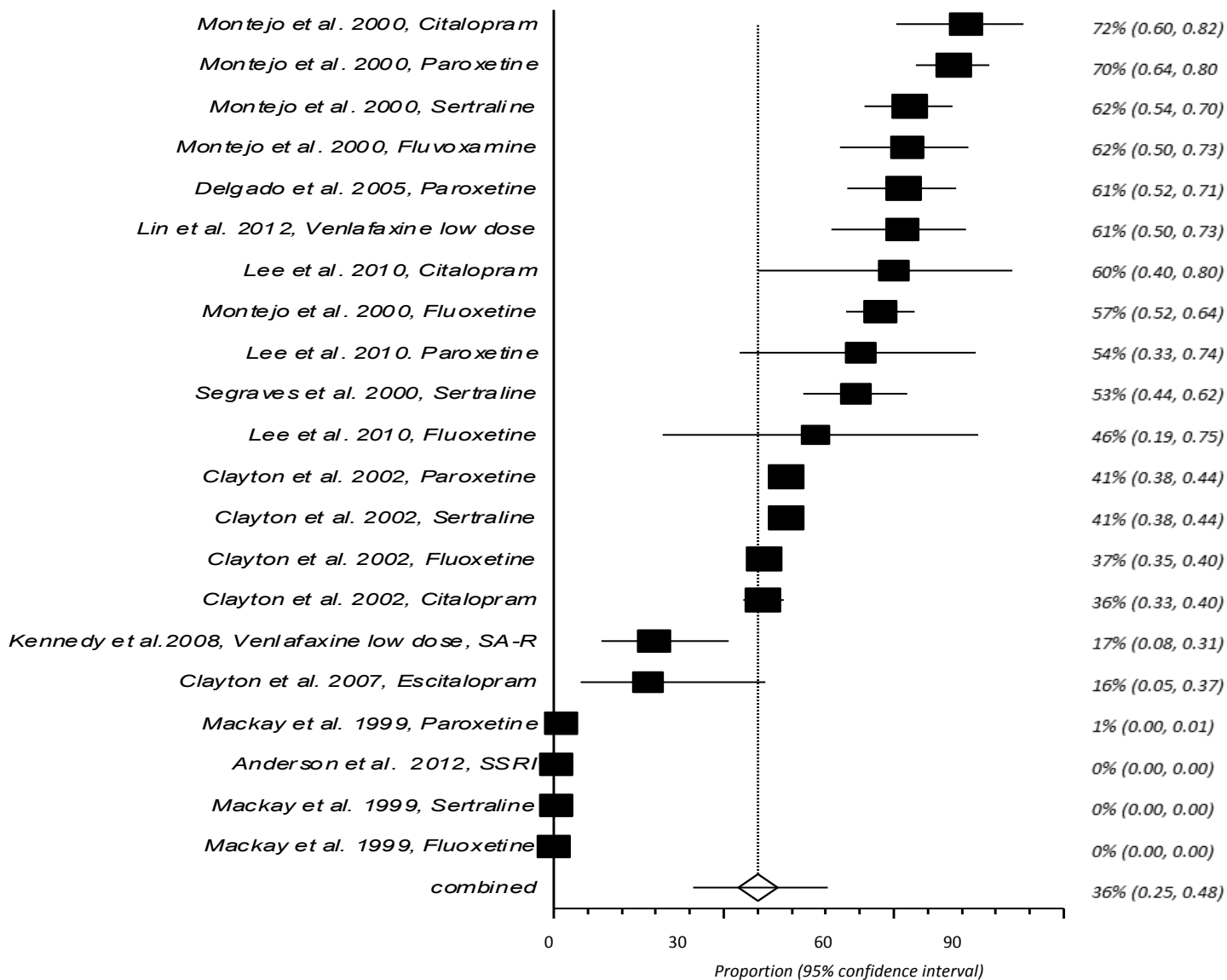
Although there were five randomized controlled studies, only four of the studies compared the non-SSRI antidepressants with SSRI or low dose venlafaxine<sup>9-12, 30</sup>. The combined relative risk of sexual dysfunction in the non-SSRI second generation antidepressant group (471 subjects) when compared with SSRI(304 subjects) was 0.57. (95% CI = 0.47to 0.68, P < 0.0001) (Figure 4). Further comparison of the pooled prevalence of sexual dysfunction between non-serotonergic (11%) and serotonergic (32%) antidepressants were shown in Figure 5 and Figure 6. Both pools had high heterogeneity. Significant statistical heterogeneity arising from methodological differences in outcome assessments suggests that the studies are not all estimating the same quantity, such as differences in prospective vs. cross-sectional study, sample-size, setting of the given study and different assessment tool used (male and female sexual functioning assessment). More importantly, some non-SSRI had very similar mechanism of action to SSRIs in the context of serotonergic pathway such as duloxetine and venlafaxine.



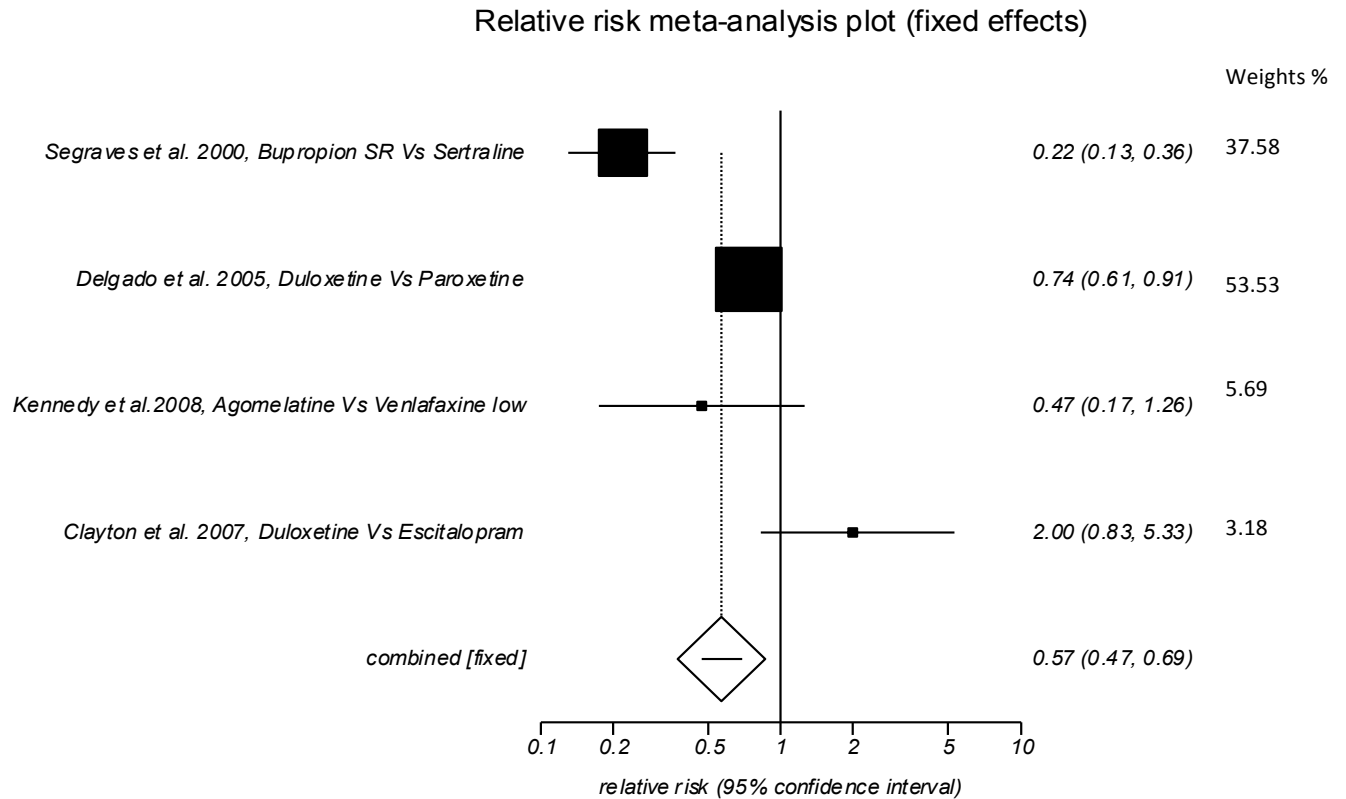
**Figure 2.** Pooled prevalence of sexual dysfunction in Agomelatine, Bupropion, Duloxetine, Venlafaxine and Mirtazapine by random effects meta-analysis. Random effects (DerSimonian-Laird) = 15% (95% CI = 0.09 to 0.21),  $I^2$  (inconsistency) = 99.2% (95% CI = 99.1% to 99.2%), Egger bias = 5.93 (95% CI = 3.17 to 8.69)  $P = 0.0002$ , Harbord bias = 23.9 (92.5% CI = 10.1 to 37.8)  $P = 0.0042$ .



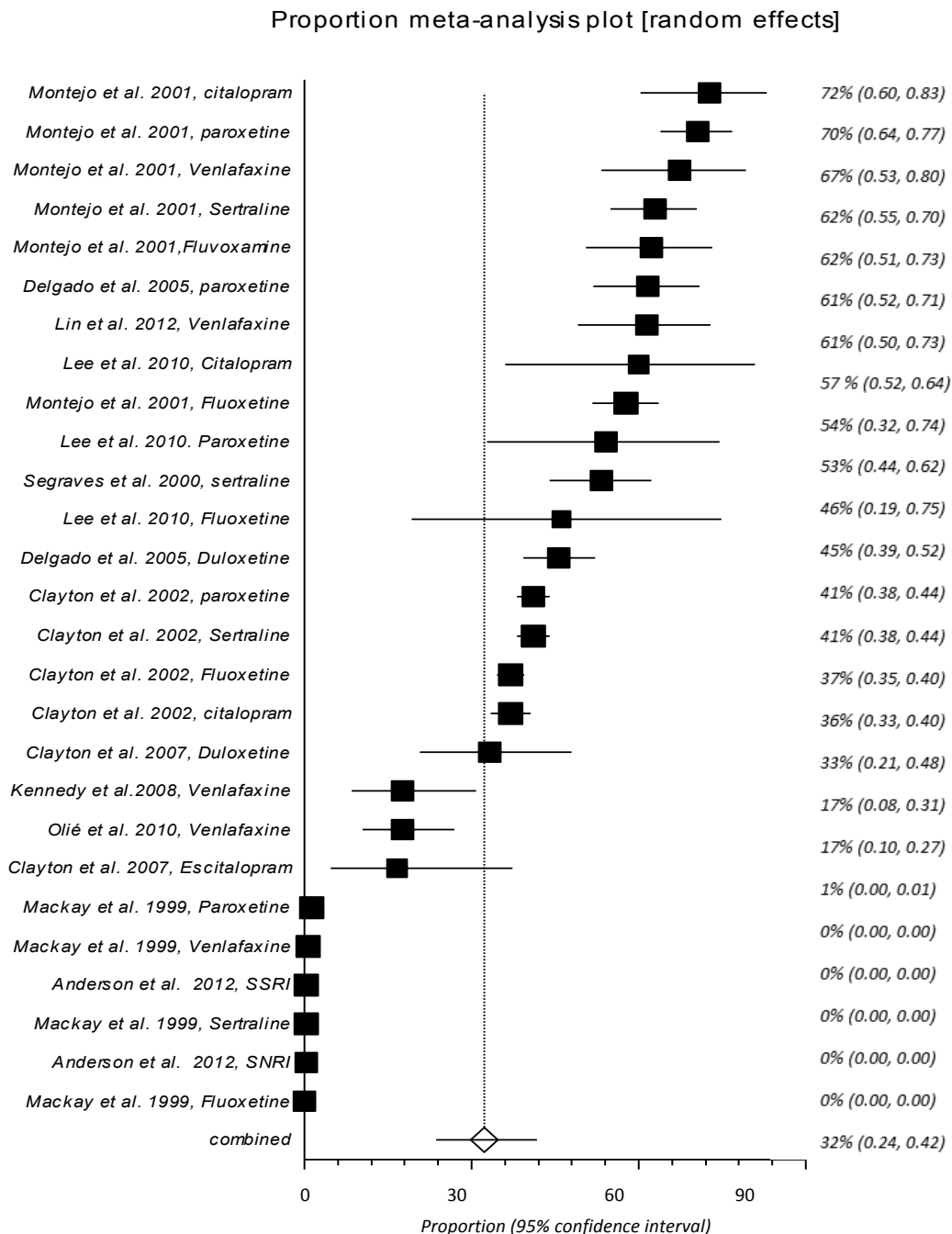
Proportion meta-analysis plot [random ef



**Figure 3.** Pooled prevalence of sexual dysfunction in SSRI group by random effects meta-analysis. Random effects (DerSimonian-Laird)= 36% (95% CI= 0.25 to 0.48),  $I^2$  (inconsistency)= 99.8% (95% CI = 99.8% to 99.8%), Egger bias = 13.5 (95% CI = 9.13 to 17.9),  $P < 0.0001$ , Harbord bias= 43.2 (92.5% CI= 26.3 to 60.18),  $P= 0.0001$ .

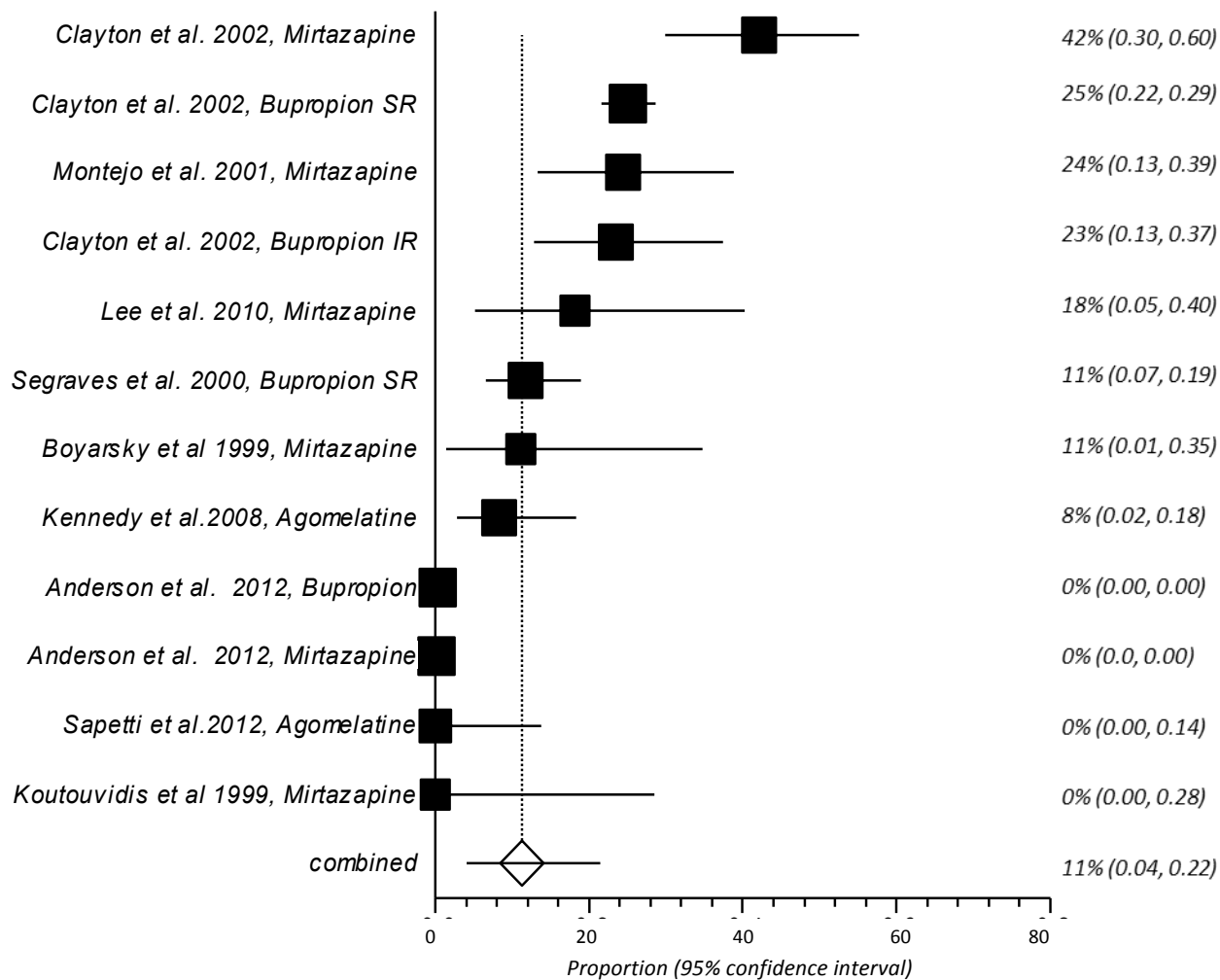


**Figure 4.** Forest plot showing meta-analyses of combined relative risk of sexual dysfunction rate when compared Bupropion SR or Duloxetine or Agomelatine with SSRI. Pooled relative risk = 0.57 (95% CI = 0.47 to 0.68,  $P < 0.0001$ ). Heterogeneity:  $I^2$  (inconsistency) = 88.3%, Egger bias = -0.85 (95% CI = -13.1 to 11.4),  $P = 0.79$ , Begg-Mazumdar Kendall's tau = -0.33,  $P = 0.33$ . RR=relative risk, CI=confidence interval.



**Figure 5.** Pooled prevalence of sexual dysfunction in serotonergic antidepressants by random effects meta-analysis. Random effects (DerSimonian-Laird)= 32% (95% CI= 0.23 to 0.41), I<sup>2</sup> (inconsistency= 99.7% (95% CI= 99.7% to 99.7%) ,Egger bias= 12.3 (95% CI= 8.8 to 15.9), P < 0.0001, Harbord bias= 42.8(92.5% CI= 27.8to 57.8), P < 0.0001.

Proportion meta-analysis plot [random effects]



**Figure 6.** Pooled prevalence of sexual dysfunction in non serotonergic antidepressants by random effects meta-analysis. Random effects (DerSimonian-Laird)= 11% (95% CI= 0.04to 0.21), I<sup>2</sup> (inconsistency)= 98.4% (95% CI= 98.2% to 98.7%), Egger bias= 3.55 (95% CI= 0.77 to 6.32), P= 0.0171, Harbord bias= 12.7 (92.5% CI = 0.24 to 25.3), P = 0.0703.

## Discussion

To our knowledge this is the first systematic review focussing on sexual side effects among agomelatine, bupropion, duloxetine, venlafaxine and mirtazapine. We found that, the pooled prevalence of sexual dysfunction in the group comprising non-SSRI second generation antidepressants was 15%, which is less than half compared to patients on SSRIs (36%). The relative risk of sexual dysfunction occurring with SSRIs was nearly twice higher when compared to non-SSRI drugs.

Sexual side effects of SSRIs are mainly attributed to its serotonergic effects which result in multiple types of sexual dysfunction in males, namely delayed ejaculation with anorgasmia<sup>30</sup>, decreased libido<sup>31</sup> and erectile dysfunction with ejaculatory disturbances<sup>32</sup> while in females inability to reach orgasm was the main complaint Feiger A et al., 1996<sup>33</sup>. The non SSRI second generation mirtazapine is the drug that has the greatest ease of orgasm and has been suggested as an alternative choice in those with orgasmic dysfunction<sup>28</sup>. This effect is due to pharmacological action at presynaptic alpha 2 adrenergic receptor antagonist and post synaptic 5HT3 receptor antagonist which promotes orgasm<sup>25</sup>.

In women all phases of sexual response cycle were evidenced to be affected by escitalopram, however only desire and arousal phases were affected by duloxetine<sup>11</sup>. This is slightly different to the data by Delgado et al which showed that orgasm is also impaired by duloxetine especially in men<sup>10</sup>.

Venlafaxine produces delayed orgasm but at a lower rate than SSRIs<sup>34</sup>. Compared to agomelatine, venlafaxine produced greater impairment in desire (agomelatine 3.6% vs

venlafaxine XR 19.4% p= 0.007). In women there was a greater deterioration in orgasm with venlafaxine (agomelatine 4.3% vs venlafaxine XR 21.2% p= 0.0001)<sup>[12]</sup>. The favorable outcome for agomelatine can be explained on the basis of its agonists affects on MT1 and MT2 receptors and 5HT2 c antagonists effects. Evidence suggests that melatonergic potentiation can promote sexual behavior while Mirtazapine was devoid of any serotonergic activity and therefore displayed low sexual dysfunction<sup>35</sup>.

We noted that the prevalence of sexual dysfunction differed from study to study. Significant statistical heterogeneity arising from methodological differences in outcome assessments suggests that the studies are not all estimating the same quantity, such as differences in prospective vs. cross-sectional study, sample-size, setting of the given study and different assessment tool used (male and female sexual functioning assessment). More importantly, some non-SSRI have very similar mechanism of action to SSRIs in the context of serotonergic pathway such as duloxetine and venlafaxine.

Another possible explanation for this is that patients from different cultural backgrounds may perceive and report sexual dysfunction differently. However, most of the studies we reviewed are from Western countries with the exception of two from Korea and Taiwan. We suspected there is a possibility of more studies done in the East but were not in English language. As sexual dysfunction in females is a neglected area in depressed patients in certain cultures<sup>36</sup>, gender differences in reporting may also contribute to the differences in prevalence found in different studies<sup>28, 37</sup>.

One of the obvious difference in prevalence across different studies can also be attributed

to the fact that different scales were used to define sexual dysfunction across the many studies, and sometimes the same scales may be utilized differently. Self administered questionnaires, due to the limitations of other methods available, remains the predominant means of sexual behavior data collection. Of the advantages of self reports, they can elicit better sexual side effects compared to direct inquiry<sup>38</sup>. The Arizona Sexual Experience Questionnaire and Change in Sexual Functioning Questionnaire (CSFQ) which were used in eight of the studies more be more appropriate as it is a patient rated questionnaire where the patient may be more willing to disclose their problems<sup>17, 39</sup>. The study by Kennedy et al<sup>40</sup> did not fulfill the requirement that both partners be present, when using the Sexual Function Questionnaire. On the other hand, though standardized questionnaires can easily elicit evidence of patterns amongst large populations, one to one interviews may be able to gather more detailed information<sup>41</sup>. However study by Mackay, 1999<sup>22</sup> limited the interview to only one question regarding impotence. Another observation that we noted was that several studies that utilized both questionnaires and interview together did not examine the level of similarity between people's questionnaire and interview responses to determine whether comparisons between these data sets are appropriate<sup>42</sup>.

It was also observed that sample sizes were markedly different across studies, with several enrolling very few patients that may result in an inability to show any effect. The prevalence among the non-SSRI second generation antidepressants themselves varied widely, ranging from 0% for Agomelatine to 67% with duloxetine. However, these differences can be explained by the different mechanism of actions of antidepressants with those relying on

serotonin may exhibit more sexual dysfunction<sup>23</sup>. For instance, agomelatine is a selective agonist of the melatonergic MT1 and MT2 receptors and 5-HT<sub>2C</sub> receptor antagonist. Even in a clinical trial used in healthy male subjects, Agomelatine has lower risk of sexual dysfunction compared to SSRI<sup>43</sup>. Mirtazepine blocks the activities at  $\alpha_2$  adrenergic and serotonergic 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors<sup>44</sup> whereas Duloxetine is a potent balanced dual reuptake inhibitor of 5-HT and NE<sup>45</sup>.

A broad search strategy to minimize the effects of biases was used. Systematic reviews are created to pool trials with differing results and present the clinician a single best estimate. They are able to overcome random errors and remove inconsistencies across the various trials being studied. As sexual problems frequently occurs as part of depression<sup>36</sup>, the studies included in this paper employed various ways in trying to differentiate between sexual impairment due to that produced by depression per se as compared to those that were due to sexual side effects of prescribed medication. This was determined by the methods designed for each individual study whether cross sectional or prospective. For example, by including patients who were either experiencing a particular side effect such as erectile dysfunction and then withdrawing them from the drug thus showing recovery and then enrolling them into the study with another drug; or participants were included when they had no sexual side effects and then assessed in a prospective manner to see if they did develop any side effects. The latter method was adopted by the majority of the studies.

We know that the mechanism of action of the antidepressants themselves are different from one another. Hence it would be better if we had been able to analyze the same

groups of antidepressants together. However this was not feasible due to the limited number of studies available for each group, especially among the newer antidepressants. In addition, different study designs and rating scales employed in the above studies pose a barrier to more meaningful comparisons. Clinicians and patients both, must be aware of the sexual adverse side effects, in all phases of sexual functioning such as decrease in sexual desire and arousal before prescribing antidepressants<sup>46</sup>. Clinicians need to be sensitive to the occurrence of SD as a common adverse event and should discuss patients' preferences before starting any therapy<sup>47</sup>.

### Conclusion

Our findings show that agomelatine and mirtazapine appear to be associated with the least occurrence of sexual dysfunction, and bupropion appears to have a possible effect on alleviating adverse sexual effects. SNRIs especially venlafaxine appears to cause sexual dysfunction on par with SSRIs. In conclusion, the pooled prevalence of sexual dysfunction in non-SSRI second generation antidepressant is lower than in SSRI antidepressants. The non-serotonergic antidepressants have lower risk of sexual dysfunction compared to the serotonergic antidepressants. Clinicians and patients should be aware of this adverse side effect before prescribing any one of them.

### Acknowledgement

None.

### Source of Funding

University Of Malaya Research Grant RP012/2012C.

### References

1. Donoghue J, Tylee A. The treatment of depression: prescribing patterns of antidepressants in primary care in the UK. *Br J Psychiatry*. 1996;168: 164-168.
2. Moore M, Yuen HM, Dunn N, Mullee MA, Maskell J, Kendrick T. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. *Bmj*. 2009;339.
3. Balon R, Yeragani VK, Pohl R, Ramesh C. Sexual dysfunction during antidepressant treatment. *J Clin Psychiatry*. 1993; 54(6): 209-212.
4. Baldwin DS, Thomas SC, Birtwistle J. Effects of antidepressant drugs on sexual function. *Int J Psychiatry Clin Pract*. 1997;1: 47-58.
5. Williams V, Baldwin DS, Hogue SL, Fehnel SE, Hollis KA, Edin HM. Estimating the prevalence and impact of antidepressant-induced sexual dysfunction in 2 European countries: a cross-sectional patient survey. *J Clin Psychiatry*. 2006;67: 204-210.
6. Williams V, Edin H, Hogue S, Fehnel S, Baldwin D. Prevalence and impact of antidepressant-associated sexual dysfunction in three European countries: replication in a cross-sectional patient survey. *J Psychopharmacol*. 2010;24: 489-496.
7. Pereira VM, Arias-Carrión O, Machado S, Nardi AE, Silva AC. Bupropion in the Depression-Related Sexual Dysfunction: A Systematic.

- CNS Neurol Disord Drug Targets. 2014;13: 1079-1088.
8. Gitlin MJ. Effects of depression and antidepressants on sexual functioning. *Bull Menninger Clin.* 1994;59: 232-248.
  9. Segraves RT, Kavoussi R, Hughes AR, et al. Evaluation of sexual functioning in depressed outpatients: a double-blind comparison of sustained-release bupropion and sertraline treatment. *J Clin Psychopharmacol.* 2000;20: 122-128.
  10. Delgado PL, Brannan SK, Mallinckrodt CH, et al. Sexual functioning assessed in 4 double-blind placebo-and paroxetine-controlled trials of duloxetine for major depressive disorder. *J Clin Psychopharmacol.* 2005;66: 686-692.
  11. Clayton A, Kornstein S, Prakash A, Mallinckrodt C, Wohlreich M. Changes in sexual functioning associated with duloxetine, escitalopram, and placebo in the treatment of patients with major depressive disorder. *J Sex Med.* 2007;4: 917.
  12. Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol.* 2008;28: 329-333.
  13. Olié J-P, Gourion D, Montagne A, Rostin M, Poirier M-F. Milnacipran and venlafaxine at flexible doses (up to 200 mg/day) in the outpatient treatment of adults with moderate-to-severe major depressive disorder: a 24-week randomized, double-blind exploratory study. *Neuropsychiatr Dis Treat.* 2010;6: 71.
  14. Clayton AH, McGarvey EL, Clavet GJ. The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. *Psychopharmacol Bull.* 1997. Jan 1;33(4):731.
  15. Quirk FH, Heiman JR, Rosen RC, Laan E, Smith MD, Boolell M. Development of a sexual function questionnaire for clinical trials of female sexual dysfunction. *J Womens Health Gend Based Med.* 2002;11: 277-289.
  16. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology.* 1997;49: 822-830.
  17. McGahuey AJG, Cindi A. Laukes, Francisco A. Moreno, Pedro L. Delgado, Kathy M. McKnight, Rachel Manber, Cynthia. The Arizona sexual experience scale (ASEX): reliability and validity. *J Sex Marital Ther.* 2000;26: 25-40.
  18. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med.* 2001;8: 1153-1157.
  19. Wen JK HC, Chen SW, Jing JH, Chu YJ. Validity and reliability of Arizona Sexual Experiences Scale-Chinese Version (ASEX-CV) in the clinical study of out-patients with



- depressive disorder and sexual dysfunction. Proceedings of the Annual Meeting of the Taiwanese Society of Psychiatry Tainan: Taiwanese Society of Psychiatry. 2006; 119-120.
20. Anderson HD, Pace WD, Libby AM, West DR, Valuck RJ. Rates of 5 common antidepressant side effects among new adult and adolescent cases of depression: A retrospective US claims study. *Clinical therapeutics*. 2012;34: 113-123.
  21. Montejo A, Garcia M, Espada M, Rico-Villademoros F, Llorca G, Izquierdo J. [Psychometric characteristics of the psychotropic-related sexual dysfunction questionnaire. Spanish work group for the study of psychotropic-related sexual dysfunctions]. *Actas espanolas de psiquiatria*. 1999;28: 141-150.
  22. Mackay F, Dunn N, Martin R, Pearce G, Freemantle S, Mann R. Newer antidepressants: a comparison of tolerability in general practice. *Br J Gen Pract*. 1999;49: 892-896.
  23. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry*. 2002;63: 357-366.
  24. Boyarsky BK, Haque W, Rouleau MR, Hirschfeld R. Sexual functioning in depressed outpatients taking mirtazapine. *Depression and anxiety*. 1999;9: 175-179.
  25. Lee K-U, Lee YM, Nam J-M, et al. Antidepressant-induced sexual dysfunction among newer antidepressants in a naturalistic setting. *Psychiatry Investig* 2010;7: 55-59.
  26. Lin C-F, Juang Y-Y, Wen J-K, Liu C-Y, Hung C-I. Correlations between sexual dysfunction, depression, anxiety, and somatic symptoms among patients with major depressive disorder. *Chang Gung Medical Journal*. 2012;35: 323-331.
  27. Koutouvidis N, Pratikakis M, Fotiadou A. The use of mirtazapine in a group of 11 patients following poor compliance to selective serotonin reuptake inhibitor treatment due to sexual dysfunction. *Int Clin Psychopharmacol*. 1999;14: 253.
  28. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. *J Clin Psychiatry*. 2001;62: 10-21.
  29. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. *J Clin Psychopharmacol*. 2009;29: 259-266.
  30. Reimherr F, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. *J Clin Psychiatry*. 1990;51(Suppl B);18-27.

31. Coleman CC, Cunningham LA, Foster VJ, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Ann Clin Psychiatry*. 1999;11: 205-215.
32. Doogan D, Caillard V. Sertraline in the prevention of depression. *Br J Psychiatry*. 1992;160: 217-222.
33. Feiger A, Kiev A, Shrivastava RK, Wisselink PG. Nefazodone versus sertraline in outpatients with major depression: Focus on efficacy, tolerability and effects on sexual function and satisfaction. *J Clin Psychiatry*. 1996; 57(2):53-62.
34. Horst WD, Preskorn SH. Mechanisms of action and clinical characteristics of three atypical antidepressants: venlafaxine, nefazodone, bupropion. *J Affect Disord*. 1998;51: 237-254.
35. Ascher JA, Cole JO, Colin J-N, et al. Bupropion: a review of its mechanism of antidepressant activity. *J Clin Psychiatry*. 1995; 56(9):395-401.
36. Sidi H, Asmidar D, Hod R, Guan NC. Female sexual dysfunction in patients treated with antidepressant—comparison between escitalopram and fluoxetine. *J Sex Med*. 2012;9: 1392-1399.
37. Sapetti A. Agomelatine: an antidepressant without deterioration of sexual response. *Sex Marital Ther*. 2012;38: 190-197.
38. McCallum EB, Peterson ZD. Investigating the impact of inquiry mode on self-reported sexual behavior: theoretical considerations and review of the literature. *J Sex Res*. 2012;49: 212-226.
39. Keller A, McGarvey EL, Clayton AH. Reliability and construct validity of the Changes in Sexual Functioning Questionnaire short-form (CSFQ-14). *Sex Marital Ther*. 2006;32: 43-52.
40. Kennedy SH, Eisfeld B, Dickens S, Bacchiochi J, Bagby R. Antidepressant-induced sexual dysfunction during treatment with moclobemide, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry*. 2000;61: 276-281.
41. Ryan F, Coughlan M, Cronin P. Interviewing in qualitative research: The one-to-one interview. *Int J Ther Rehabil*. 2009;16: 309-314.
42. Harris LR, Brown GTL. Mixing interview and questionnaire methods: Practical problems in aligning data. 2010.
43. Montejo A, Prieto N, Terleira A, et al. Better sexual acceptability of agomelatine (25 and 50 mg) compared with paroxetine (20 mg) in healthy male volunteers. An 8-week, placebo-controlled study using the PRSEXDQ-SALSEX scale. *J Psychopharmacol*. 2010;24: 111-120.
44. Stahl S, Zivkov M, Reimitz P, Panagides J, Hoff W. Meta-analysis of randomized, double-blind, placebo-controlled, efficacy and

- safety studies of mirtazapine versus amitriptyline in major depression. *Acta Psychiatr Scand.* 1997;96: 22-30.
45. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology.* 2001; 25: 871-880.
46. Midi M, Kanagasundram S, Sidi H, Asmidar D, Naing L, Guan NC. Sexual Arousal Difficulties in Women Treated with Antidepressants: A Comparison between Escitalopram and Fluoxetine. *Int J Psychiatry Med.* 2012;43: 405-418.
47. Reichenpfader U, Gartlehner G, Morgan LC, et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. *Drug Saf.* 2014;37: 19-31.

**Corresponding Author**

Associate Professor Dr. Anne Yee  
Department of Psychological Medicine,  
Psychological Medicine Research Group of University Malaya (PARADIGM),  
Faculty of Medicine, University Malaya,  
50603 Kuala Lumpur, Malaysia  
**Tel:**+60379493049

**Email:** annyee17@um.edu.my