**Antidepressants causing sexual problems? Give her Viagra. *J Fam Pract*. 2008;57:793-796.**
**Potential PURL Review Form: Randomized controlled trials**
**SECTION 1: IDENTIFYING INFORMATION FOR NOMINATED POTENTIAL PURL**

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| **1.0** Citation | Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *JAMA*. 2008;300(4):395-404. |
| **1.1** Hypertext link to PDF of full article | http://jama.ama-assn.org/cgi/reprint/300/4/395 |
| **1.2** First date published study available to readers | July 2008 |
| **1.3** PubMed ID | 18647982 |
| **1.4** Nominated By | Sarah-Anne Schumann |
| **1.5** Institutional Affiliation of Nominator | University of Chicago |
| **1.6** Date Nominated | 7/22/08 |
| **1.7** Identified Through | *JAMA* |
| **1.8** PURLS Editor Reviewing Nominated Potential PURL | Bernard Ewigman |
| **1.9** Nomination Decision Date | 7/23/08 |
| **1.10** Potential PURL Review Form (PPRF) Type | RCT |
| **1.12** Assigned Potential PURL Reviewer | Debra B. Stulberg |
| **1.13** Reviewer Affiliation | University of Chicago |
| **1.14** Date Review Due | 7/30/08 |
| **1.15** Abstract | **Context** Antidepressant-associated sexual dysfunction is a common adverse effect that frequently results in premature medication treatment discontinuation and for which no treatment has demonstrated efficacy in women.<br><br>**Objective** To evaluate the efficacy of sildenafil for sexual dysfunction associated with selective and nonselective serotonin reuptake inhibitors (SRIs) in women. |

**Design, Setting, and Participants** An 8-week prospective, parallel-group, randomized, double-blind, placebo-controlled clinical trial conducted between September 1, 2003, and January 1, 2007, at 7 US research centers that included 98 previously sexually functioning, premenopausal women (mean [SD] age 37.1 [6] years) whose major depression was remitted by SRIs but who were also experiencing sexual dysfunction.

**Intervention** Forty-nine patients were randomly assigned to take sildenafil or placebo at a flexible dose starting at 50 mg adjustable to 100 mg before sexual activity.

**Main Outcome Measures** The primary outcome measure was the mean difference in change from baseline to study end (ie, lower ordinal score) on the Clinical Global Impression sexual function scale. Secondary measures included the Female Sexual Function Questionnaire, the Arizona Sexual Experience scale-female version, the University of New Mexico Sexual Function Inventory-female version, a sexual activity event log, and the Hamilton Depression Rating scale. Hormone levels were also assessed.

**Results** In an intention-to-treat analysis, women treated with sildenafil had a mean Clinical Global Impression–sexual function score of 1.9 (95% confidence interval [CI], 1.6-2.3) compared with those taking placebo (1.1; 95% CI, 0.8-1.5), with a mean end point difference of 0.8 (95% CI, 0.6-1.0; *P*=.001). Assigning baseline values carried forward to the 22% of patients who prematurely discontinued resulted in a mean end point in the sexual function score of 1.5 (95% CI, 1.1-1.9) among women taking sildenafil compared with 0.9 (95% CI, 0.6-1.3) among women taking placebo, with a mean end point difference of 0.6 (95% CI, 0.3-0.8; *P*=.03). Baseline endocrine levels were within normal limits and did not differ between groups. The mean (SD) Hamilton scores for depression remained consistent with remission in both groups (4.0 [3.6]; *P*=.90). Headache, flushing, and dyspepsia were reported frequently during treatment, but no patients withdrew because of serious adverse effects.

**Conclusion** In this study population, sildenafil treatment of sexual dysfunction in women taking SRIs was associated with a reduction in adverse sexual effects.

**Trial Registration** clinicaltrials.gov Identifier: NCT00375297

**Author Affiliations:** Department of Psychiatry, Health Sciences Center, University of New Mexico School of Medicine, Albuquerque (Drs. Nurnberg and Hensley, and Ms. Paine); The Croft Group, San Antonio, Texas (Dr. Croft); the Kinsey Institute for Research in Sex, Gender, and Reproduction, Indiana University, Bloomington (Dr. Heiman); and Stanford University School of Medicine, Palo Alto, California (Dr. Debattista).

**1.16** Pending PURL Review Date 7/31/08

**SECTION 2: CRITICAL APPRAISAL OF VALIDITY**

**2.1** Number of patients starting each arm of the study?

49 in sildenafil arm, 49 in placebo arm

**2.2** Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?

<u>Inclusion criteria:</u>

- Women ages 18-50
- Premenopausal (Although this was a stated criterion, Table 1 says only 89.8% in the placebo group and 77.6% in the sildenafil group were actually premenopausal)
- Diagnosis of major depression in remission, defined as Hamilton Rating Scale for Depression score ≤10 where max score is 68, <7 is usually considered normal, and >20 is moderately severe depression. (Again, Table 1 states a small number of participants had other depressive disorders, not major depression)
- Taking an antidepressant with a selective or nonselective serotonin reuptake inhibition (SRI) mechanism for at least 8 weeks with a stable dose for at least 4 weeks
- Experiencing persistent sexual dysfunction for at least 4 weeks (meeting DSM-IV criteria for substance-induced sexual dysfunction)
- In good health
- Had some form of sexual activity (masturbation or with partner) at least twice monthly before antidepressant therapy
- Willing to continue efforts at sexual activity at least once weekly for duration of the study
- Satisfactory sexual function before onset of depression or any antidepressant treatment
- If any episodes of prior sexual dysfunction, limited to previous episodes of depression or antidepressant therapy and remitting when depression/tx episode ends

<u>Exclusion criteria</u>:

- Diagnosis of a sexual disorder other than one associated with SRI treatment or depression
- Genital anatomic deformity
- Hysterectomy
- Uncontrolled psychiatric disorder; Hamilton Rating Scale for Anxiety score >10
- Comorbidities: diabetes, cardiovascular disease, alcohol or substance abuse or dependence, stroke, unstable cardiac condition, arrhythmia, MI within last 6 months, current or anticipated use or nitrates, or proliferative retinopathy
- Major relationship changes

- Investigative drug use within 3 months
- Current use of other treatments for sexual dysfunction
- A partner with sexual dysfunction
- Change in SRI antidepressant dose during study
- Use of hormone therapy (according to Table 1, 33% of the placebo group and 38% of the sildenafil group were on hormonal contraceptives)
- Pregnancy, lactation, or planning to become pregnant during study
- Childbearing potential and unwilling, unprepared or judged unreliable to use an acceptable and verifiable form of contraception during the trial
- Pap test indicating need for further assessment
- Dyspareunia due to other medical causes
- Amenorrhea >1 year
- Situational sexual dysfunction

Demographics:

- Age mean (SD): 36.1 years (7.6) in placebo group, 37.4 (6.6) in sildenafil
- Married or with significant other: 83.7% in placebo group, 93.4% in sildenafil
- ≥ high school education: 85.7% in placebo group, 87.8% in sildenafil
- Number of children, mean (SD): 1.2 (1.2) in placebo group, 1.3 (1.3) in sildenafil

Baseline morbidity:

- Primary diagnosis of major depression: 98% in placebo group, 96% in sildenafil (remainder have dysthymia, depressive disorder NOS, or anxiety with depression)
- Months of antidepressant use, mean (SD): 25.8 (33.8) placebo group, 29.3 (35.6) sildenafil group
- Smokers: 14.3% placebo, 16.3% sildenafil
- Drink alcohol: 87.8% placebo, 81.6% sildenafil
- Mean (SD) number of sexual problems: 2.8 (0.7) in placebo group, 3.0 (0.7) in sildenafil
- Libido problems: 87.8% placebo, 87.8% sildenafil
- Arousal difficulty or lubrication problems: 77.6% placebo, 83.7% sildenafil
- Anorgasmia: 16.3% placebo, 28.6% sildenafil ($P$=.15)
- Orgasm delay: 97.6% placebo, 100% sildenafil
- Sexual attempts within 30 days, mean (SD): 6.1 (5.6) placebo, 6.0 (4.8) sildenafil
- % of sexual attempts successful: 34.7 (37.1) placebo, 24.6 (31.9) sildenafil
- Normal levels of hormones: cortisol, estradiol, FSH, LH, progesterone, prolactin, SHBG, total testosterone, free testosterone, TSH, T4

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| | Setting:<br>• 7 US outpatient clinic medical centers: University of New Mexico, University of Washington, Stanford, University of Oklahoma, RWJ University of Medicine and Dentistry of New Jersey, Croft Research Center San Antonio, Massachusetts General Hospital<br>• Participants recruited from outpatient settings, newspaper ads, postings, and referrals. |
| **2.3** Intervention(s) being investigated? | Sildenafil 50 mg, take 1 tablet approximately 1-2 hours before anticipated sexual activity not more than once daily; investigators could increase dose to 2 tabs based on judgment of efficacy and tolerability |
| **2.4** Comparison treatment(s), placebo, or nothing? | Placebo |
| **2.5** Length of follow up? Note specified end points, eg, death, cure, etc. | Assessed at baseline, 2 weeks, 4 weeks, and 8 weeks. In the placebo group 75.5% completed 8 weeks of follow up vs 79.6% in the sildenafil group. All participants completed at least 1 assessment after baseline. For those not completing all 8 weeks, the end point was defined as the last recorded assessment (2 or 4 weeks). A separate (more conservative) analysis was done using the baseline characteristic as the outcome for those not completing all 8 weeks. |
| **2.6** What outcome measures are used? List all that assess effectiveness. | Primary outcome: Change from baseline to end point in Clinical Global Impression scale adapted for sexual function. This scale is a clinician rating based on review of patient diary and discussion with patient. Scale is 1=normal function, 7=most extreme sexual dysfunction.<br>Other outcomes:<br>• Change in Sexual Function Questionnaire (SFQ) score, a 34-item patient-rated self-report scale measuring 7 functional domains: desire, arousal-sensation, arousal-lubrication, orgasm, enjoyment, pain, partner. Higher score means better sexual function. Total score range is 5-31.<br>• Change in Arizona Sexual Experience Scale (ASEX), a 5-item patient-rated scale measuring 5 domains: sexual drive, arousal (subjective excitement), lubrication (physiological excitement), ability to reach orgasm, orgasm satisfaction. Higher score means worse dysfunction. Total score range is 5-30.<br>• Change in University of New Mexico Sexual Function Inventory (UNM-SFI), a 5-item clinician-rated scale with domains, scoring, and scale very similar to ASEX. Higher score means worse dysfunction.<br>• Change in Hamilton Rating Scale for Depression score<br>• Change in hormone levels |

**2.7** What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, *P*-values, etc.

Primary Outcome, intent-to-treat last-observation-carried-forward analysis: On the 7-point Clinical Global Impression scale (7 = extreme dysfunction), placebo users improved from a mean baseline of 4.7 to a mean end point of 3.6 (mean change from baseline = 1.10), while sildenafil users changed from a mean baseline of 4.8 to a mean end point of 2.8 (mean change from baseline = 1.91). The difference between treatment and placebo was 0.8, 95% CI, 0.6-1.0; *P*=.001.

Primary Outcome, intent-to-treat baseline-carried-forward analysis: Placebo users improved from a mean baseline of 4.7 to a mean end point of 3.8 (mean change from baseline = 0.9), while sildenafil users changed from a mean baseline of 4.8 to a mean end point of 3.2 (mean change from baseline = 1.5). The difference between treatment and placebo was 0.6, 95% CI, 0.3-0.8; *P*=.03.

Improvement yes vs no (no improvement defined as score >3 at end point): No improvement in 73% in placebo group, 28% in sildenafil group. (If we want to define this outcome as "presence of sexual dysfunction" we can calculate an Absolute Risk Reduction of 73-28 = 45% and get a NNT of 1/0.45 = 2.2)

Secondary outcomes:

- Change in SFQ: In the domains of orgasm, enjoyment, and partner, sildenafil is statistically significantly favored over placebo, with effect sizes small. For example, in the Enjoyment domain, where scores range from 6 (lowest enjoyment) to 30 (highest), placebo users improved from 14.3 to 16.9, sildenafil users from 13.0 to 18.0; difference is 2.4 points, *P*=.05.
- Change in ASEX: In the domains of ability to reach orgasm and orgasm satisfaction, sildenafil is statistically significantly favored. In the total score, range is 5-30, with 30 being the worst function: placebo users improved from 21.9 to 20.0, sildenafil users from 22.9 to 19.5, for a treatment difference of 1.5 (95% CI, –0.1 to 3.1; *P*=.06)
- Change in UNM-SFI: Only the domain Ability to reach orgasm showed a statistically significant benefit of sildenafil. Overall satisfaction domain, and total score, favor sildenafil and almost reach statistical significance.
- Hamilton Rating Scale for Depression scores did not show statistically or clinically significant changes from baseline to end point in either group, and there was no intergroup difference.
- Independent of treatment vs placebo group assignment, comparing those whose sexual function improved to those whose did not showed higher mean baseline levels of free testosterone (*P*<0.01) and thyroxine (T4) (*P*<.01).

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| | Adverse Events:<br>• Headache, visual disturbance, dyspepsia, flushing, nasal congestion, palpitations and insomnia were all more common in the sildenafil group<br>• Nausea was more common in the placebo group<br>• Fairly common adverse events in the sildenafil group include headache (43% in sildenafil vs 27% in placebo group); flushing (24% in sildenafil, 0 in placebo), and nasal congestion (37% in sildenafil vs 6% in placebo group) |
| **2.8** Study addresses an appropriate and clearly focused question - ***select one*** | ☒ Well covered ☐ Not addressed<br>☐ Adequately addressed ☐ Not reported<br>☐ Poorly addressed ☐ Not applicable |
| **2.9** Random allocation to comparison groups | Well covered |
| **2.10** Concealed allocation to comparison groups | Well covered |
| **2.11** Subjects and investigators kept "blind" to comparison group allocation | Well covered |
| **2.12** Comparison groups are similar at the start of the trial | Well covered |
| **2.13** Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias. | Well covered<br>Comments: There is a difference in the rate of anorgasmia: 28.6% of the sildenafil group reported this symptom at baseline vs 16.3% in the placebo group, *P*=.15. This could arguably bias the results slightly towards the treatment group, but given the consistency of other symptoms (eg, 98% and 100% reported orgasm delay, 88% in both groups reported libido problems) and the multiple domains of outcomes measured, this doesn't bother me much |
| **2.14** Were all relevant outcomes measured in a standardized, valid, and reliable way? | Well covered |

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| **2.15** Are patient-oriented outcomes included? If yes, what are they? | All the outcomes are patient-oriented measures of sexual function |
| **2.16** What percent dropped out, and were lost to follow up? Could this bias the results? How? | All participants had at least one assessment measurement (at 2, 4, or 8 weeks). In the placebo group, 12 of 49 (24.5%) discontinued prior to the 8-week point. Nine discontinued because of a lack of efficacy, 3 were lost to follow-up. In the sildenafil group, 10 of 49 (20.4%) discontinued prior to 8 weeks. Four discontinued because of a lack of efficacy, 6 were lost to follow-up. The overall numbers of drop-outs are similar enough to avoid bias. If anything, the fact that more in the placebo group dropped out for lack of efficacy than in the sildenafil group biases the (intention-to-treat) findings towards the null. |
| **2.17** Was there an intention-to-treat analysis? If not, could this bias the results? How? | Yes |
| **2.18** If a multi-site study, are results comparable for all sites? | Not reported |
| **2.19** Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity? | Funded by an investigator-initiated grant from Pfizer, the maker of Viagra. The article says Pfizer had no part in study design, data, or manuscript review. I guess we have to believe them. |
| **2.20** To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized. | Patients in the study were on long-term SRI treatment for depression, with their disease well-controlled (in remission while on treatment). Other than their depression, they were healthy, mostly pre-menopausal women. They had sexual dysfunction that could only be attributed to the depression or meds, not to other causes. |
| **2.21** In what care settings might the findings apply, or not apply? | Outpatient family med centers, assuming providers are able to assess the specific varieties of sexual dysfunction |
| **2.22** To which clinicians or policy makers might the findings be relevant? | Primary care providers and psychiatrists in outpatient settings; payers deciding what therapies to cover |

## SECTION 3: REVIEW OF SECONDARY LITERATURE

**3.1** DynaMed excerpts

In a section on SSRI-related sexual dysfunction, DynaMed summarizes the 2004 Cochrane review which concluded sildenafil is effective in men but otherwise found no well-supported treatment strategies. DynaMed also summarizes a Clinical Inquiry from 2002, which found that augmentation and drug holidays have little to no RCT support, while substitution with nefazodone, bupropion, or mirtazapine was shown beneficial in randomized trials. Finally, DynaMed reports the findings of several individual studies which support the conclusions of the above evidence-based reviews.

**3.2** DynaMed citation/access date

http://dynaweb.ebscohost.com/Detail.aspx?docid=/dynamed/d6623b8eb8438c8f86256c40007e8bff&sid=f1bff55a-de28-4fb0-a8a0-4c94effc2290@sessionmgr2 accessed 7/23/08. Article on Antidepressants.

**3.3** UpToDate excerpts

Several strategies for treatment of SSRI-related sexual dysfunction are offered in UpToDate, including dose changes, switching to another medication, drug holidays, and augmentation with a second drug. No evidence is offered to support these strategies other than the RCT of sildenafil in men. UpToDate mentions that published studies on augmenting with a second medication other than sildenafil have been nonrandomized trials or case series.

**3.4** UpToDate citation/access date

http://www.uptodateonline.com/online/content/topic.do?topicKey=psychiat/10135&selectedTitle=2~150&source=search_result accessed 7/23/08. Article entitled “Sexual dysfunction associated with selective serotonin reuptake inhibitor (SSRI) antidepressants,” last updated 6/07

**3.5** PEPID PCP excerpts

**What are treatment options for SSRI-related sexual dysfunction?**
**Evidence-Based Answer** *(Pub **8/2002**)*

1. Substituting an antidepressant with lower incidence of sexual dysfunction such as bupropion, nefazodone, or mirtazapine is beneficial. (GOR: B – based on RCTs)
    - Augmentation therapy with amantadine, bupropion, and amantadine is no better than placebo. (GOR: B, based on RCTs)
    - Augmentation therapy with multiple other agents may be beneficial. (GOR: D, open-label, nonrandomized studies; case series; and case reports)
    - SSRI “drug holidays” may also be effective. (GOR: D, open-label, nonrandomized studies.) (Table)

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| **3.6** PEPID citation/access data | http://www.pepidonline.com/Main.aspx accessed 7/23/08. PEPID seems to have no entry for female sexual dysfunction, only male sexual dysfunction and specific syndromes such as low libido or pain with intercourse. Under depression, it lists the related Evidence-Based Inquiries, and the first one is about treatment of SSRI-related sexual dysfunction. |

**SECTION 4: CONCLUSIONS**

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| **4.1 Validity:** How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) | 1 |
| **4.2** If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results? | |
| **4.3 Relevance:** Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) | 2 |
| **4.4** If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation. | |
| **4.5 Practice-changing potential:** If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice) | 1 |

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| **4.6** If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population, and the expected benefit. | Women with depression that is well controlled on chronic SSRI or SNRI therapy who have sexual dysfunction secondary to their antidepressant should be offered sildenafil. |
| 4.7 Applicability to a Family Medical Care Setting:<br>Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention? Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting) | 1 |
| **4.8** If you coded 4.7 as a 4, 5, 6 or 7, please explain. | |
| **4.9.** Immediacy of Applicability: Is this change immediately applicable in practice? Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied) | 1 |
| **4.10** If you coded 4.9 as 4, 5, 6, or 7, please explain why. | |
| **4.11** In your opinion, is this a Pending PURL? Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL) | 2 |

Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting
- Immediacy of applicability

**4.12 Comments on your response in 4.11**

The finding is new – it has been demonstrated in men previously, but not in women. It seems to be valid (for a narrow group of women), relevant, and applicable. However, the trial was small (98 participants) and the effect sizes may be considered small depending on how you look at them. In the primary outcome, sildenafil users improved from 4.8 to 2.8 on a 7-point (1=normal, 7=extreme dysfunction) scale, while placebo users improved from 4.7 to 3.6. Another way of measuring outcomes, the percent with dysfunction (score >3) after treatment was 73% in the placebo group versus 28% in the sildenafil group, giving a great-sounding NNT of 2. In the domains of low libido and difficulty with arousal, many women experienced these symptoms at baseline, and both sildenafil and placebo were effective: sildenafil more so, but not reaching statistical significance. In the domain of orgasm delay (also a very common symptom) or satisfaction with orgasm, sildenafil is statistically significantly better. So, for me, the bottom line is I tend to believe their findings are true and if so, they do have the potential to help some patients. But the group it applies to is small (I, for example, do not have any patients who have been on SSRIs for 25 months), the study is small, and the size of the effect is debatable. I would want my colleagues to know this is an option worth trying, but I would also want larger/broader studies (and a review of unpublished trials) before I would view it as an effective therapy.

## SECTION 5: EDITORIAL DECISIONS

**5.1** FPIN PURLs editorial decision (select one)

Pending PURL

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| **5.3** FPIN PURLS Editor making decision | Bernard Ewigman |
| **5.4** Date of decision | 7/31/08 |
| **5.5** Brief summary of decision | This small RCT shows that sildenafil is effective for women with sexual dysfunction on SSRIs who have well-controlled depression, the first such study to show this result. The effect sizes are not dramatic, but seem clinically important: sildenafil users improved from 4.8 to 2.8 on a 7-point (1=normal, 7=extreme dysfunction) scale, while placebo users improved from 4.7 to 3.6. The percent with dysfunction (score >3) after treatment was 73% in the placebo group versus 28% in the sildenafil group, giving a great-sounding NNT of 2. In the domains of low libido and difficulty with arousal, many women experienced these symptoms at baseline, and both sildenafil and placebo groups improved: sildenafil more so, but not reaching statistical significance. In the domain of orgasm delay (also a very common symptom) or satisfaction with orgasm, sildenafil is statistically significantly better. This study seems to be valid and this option may help some women, though the group may be small (these subjects had been on SSRIs for 25 months). This option seems worth trying, although a review of unpublished trials and replication would more convincingly establish this strategy as an effective intervention. |