CPD Online summary note

Antidepressants and psychosexual dysfunction: Part 2 – Treatment

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In this module, we have learned about how to reverse antidepressant-induced sexual dysfunction by either adjusting antidepressive treatment or by reversing specific undesirable neurotransmitter and second messenger effects. We have further learned about hormone treatments and complementary medicines for sexual dysfunction. Finally, we explored the principles of prescribing of medicines without a license or outside the remit of their current license.

Here are the key points to remember:

- For patients who value their sexual function highly, antidepressant-associated sexual dysfunction should be recognised and if possible treated.
- An antidepressant associated with a low prevalence of sexual dysfunction could be prescribed as first-line treatment.
- Substitution of a possible suspect offending agent by using an alternative antidepressant with less impact on sexual function should be considered for those patients who already receive antidepressants and suffer from sexual dysfunction. An appropriate 'swapping and stopping' regimen must be observed when switching over to reduce the likelihood of additive effects, e.g. serotonin syndrome.
- Antidepressants that are less likely to be associated with sexual dysfunction include:

  - non-serotonergic antidepressants such as reboxetine and bupropion
  - substances with $5HT_2$ blocking properties such as trazodone and mirtazapine
  - drugs that strike a balance between serotonin and NA reuptake such as duloxetine.

Reversing sexual dysfunction pharmacologically by targeting specific receptors is a further treatment option. However, this may not be successful for antidepressants mediating sexual dysfunction through several receptors and neurotransmitters.

- At present, trial evidence is limited for most substances except for oral treatments of erectile dysfunction.
- Agents licensed for the treatment of erectile dysfunction include sublingual apomorphine and $phoshodiesterase_5$ inhibitors such as sildenafil, tadalafil and vardenafil. PD_5 inhibitors impair the breakdown of cyclic guanosine monophosphate (cGMP), the production of which is mediated by nitric oxide.

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- Generally they are contraindicated in men in whom sexual activity is medically inadvisable, e.g. who suffer from severe cardiovascular disease.

- PD_5 inhibitors are specifically contraindicated in men who take nitrates including amylnitrate (poppers) because fatal hypotension can occur.

- Finally, PD_5 inhibitors are contraindicated in patients with hereditary degenerative retinal disturbances such as retinitis pigmentosa.

- Sildenafil and Vardenafil may not work if they are taken after a meal.

- Sublingual apomorphine may not work if the tablet is swallowed instead of dissolved under the tongue.

- In the UK, treatments for erectile dysfunction may only be prescribed at the expense of the NHS if they meet the prescribing criteria outlined in the BNF.

Hormonal treatments are used for the treatment of hypoactive sexual desire disorder (HSDD), but the role of hormone supplementation in the treatment of antidepressant induced sexual dysfunction remains unclear.

- All hormone replacement therapies (HRT) may promote the growth hormone sensitive cancer cells. HRT is also associated with an increased cardiovascular risk so that risks and benefits must be carefully considered before treatment is initiated.

- Men with an elevated prostate specific antigen (PSA) must not be prescribed testosterone.

- Testosterone is associated with an increased risk of depression and DHEA with an increased risk of mania.

Complementary therapies should be carefully evaluated in regard to potential risks and treatment recommendation must be based on an individual circumstances.

- Many complementary treatments may have psychotropic properties and /or interact with antidepressants. Some such as ginseng and ginkgo may precipitate hypomanic episodes in vulnerable people.

Doctors who prescribe substances that are either not licensed at all or not licensed for the treatment of sexual dysfunction must follow the practice guidance of their respective professional bodies.

Lookup tables from the module are provided on the following pages.

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Pharmacological reversal – target noradrenaline

Substance	Strategy	Mechanism of action	Comment
Reboxetine	Alternative antidepressant	NA reuptake inhibition	Not licensed (NL) in the US as an antidepressant
Bupropion	Alternative antidepressant	NA reuptake inhibition	NL in the UK as an antidepressant
Duloxetine	Alternative antidepressant	NA reuptake inhibition	
Mirtazapine	Alternative antidepressant	α_2-adrenoceptor blockade	
Yohimbine	Targeted pharmacological reversal	α_2-adrenoceptor blockade α_1-blockade peripherally	NL for treatment of sexual dysfunction

Pharmacological reversal – target serotonin

Substance	Strategy	Mechanism of action	Comment
Duloxetine	Alternative antidepressant	Serotonin reuptake inhibition	
Mirtazapine	Alternative antidepressant	$5HT_2$ and $5HT_3$ blockade	
Trazodone	Alternative antidepressant	$5HT_2$ blockade	Rare occurrence of priapism
Olanzapine	Alternative antidepressant	$5HT_2$ blockade	Not found to be effective for the reversal of sexual dysfunction
Cyproheptadine	Targeted pharmacological reversal	$5HT_2$ blockade	NL for the treatment of sexual dysfunction
Granisetron/ sumatriptan	Targeted pharmacological reversal	$5HT_3$ blockade	NL for the treatment of sexual dysfunction

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Pharmacological reversal – target dopamine

Substance	Strategy	Mechanism of action	Comment
Bupropion	Alternative antidepressant	DA reuptake inhibition	Not licensed in the UK as an antidepressant
Apomorphin	DA increase	DA agonist	Licensed as a sublingual formulation for the treatment of erectile dysfunction (Uprima®)
Amantadine	DA increase	DA agonist	Psychiatric side effects NL for the treatment of sexual dysfunction

Pharmacological reversal - other targets

Substance	Strategy	Mechanism of action	Comment
Neostigmine/ Physiostigmine	Targeted pharmacological reversal	Acetylcholinesterase inhibition	Case reports of men with spinal cord injuries only, NL for the treatment of sexual dysfunction
Betanechol	Targeted pharmacological reversal	Acetylcholinesterase inhibition cGMP increase	NL for the treatment of sexual dysfunction
Loratidine	Unclear	Unclear, H_1 antagonist	NL for the treatment of sexual dysfunction

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Pharmacological reversal – target nitric oxide (NO)

Substance	Strategy	Mechanism of action	Comment
Sildenafil Viagra ®	NO increase	PD_5 * inhibition	Take before meals
Tadalafil Cialis ®	NO increase	PD_5 inhibition	Long half life
Vardenafil Levitra ®	NO increase	PD_5 inhibition	Take before meals
*Phosphodieasterase$_5$ inhibition			

References

Basaria, S., Dobs, A.S. (2006) Clinical review: Controversies regarding transdermal androgen therapy in postmenopausal women. *J Clin Endocrine Metab*, **91**:4743-4752

British Medical Association and Royal Pharmaceutical Society of Great Britain British National Formulary, **53*, *March 2007**

Buvat, J. (2003) Androgen therapy with dehydroepiandrosterone. *World J Urol*, **21**:346-355

Clayton, A.H., Zajecka, J., Ferguson, J.M. et al (2003) Lack of sexual dysfunction with the selective noradrenaline reuptake inhibitor reboxetine during treatment for major depressive disorder. *Int Clin Psychopharmacol*, **18**:151-156

Cohen, M.H. and Eisenberg, D.M. (2002) Potential physician malpractice liability associated with complementary and integrative medicinal therapies. *Ann Intern Med*, **136**:596-603

Drug and Therapeutics Bulletin (2004) *New oral drugs for erectile dysfunction.* **42(7)**:49-52

Fonseca, A.M., Bagnoli, V.R., Penteado, S.R., Paixão, J.S., Cavalcanti, A.L., Pinotti, J.A. (2007) Monophasic estrogen-progestogen therapy and sexuality in postmenopausal women. *Clin Drug Investig*, **27**:131-137

Gelenberg, A.J., McGahuey, C., Laukes, C. et al (2000) Mirtazapine substitution in SSRI-induced sexual dysfunction. *J Clin Psychiatry*, **61**:356-360

General Medical Council (2006) Good Practice for Prescribing Medicines.

Ito, T.Y., Polan, M.L., Whipple, B., Trant, A.S. (2006) The enhancement of female sexual function with ArginMax, a nutritional supplement, among women differing in menopausal status. *J Sex Marit Ther,* **32**:369-378

Ito, T., Kawahara, K., Das, A. and Strudwick, W. (1998) The effects of ArginMax, a natural dietary supplement for enhancement of male sexual function. *Hawaii Med J,* **57**:741-744

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Kingsberg, S. (2007) Testosterone treatment for hypoactive sexual desire disorder in postmenopausal women. *J Sex Med*, **4 (Supp 3)**:227-234

Läkemedelsverket [Swedish Medicines Control Agency] (2007) Intrinsa Monograph. *Information från läkemedelsverket*. **3**:35-37

Michelson, D., Kociban, K., Tamura, R. et al (2002) Mirtazapine, yohimbine or olanzapine augmentation therapy for serotonin reuptake-associated female sexual dysfunction: a randomized, placebo controlled trial. *J Psychiatr Res,* **36**:147-152

Montorsi, F., Salonia, A., Deho, F. et al (2003) Pharmacological management of erectile dysfunction. *BJU Int* , **91**:446-454

Natural Medicines Comprehensive Database (2007)

Nelson, H.D., Humphrey, L.L., Nygren, P., Teutsch, S.M., Allan, J.D. (2002) Postmenopausal hormone replacement therapy: scientific review. *JAMA*, **288**:872-881

NHS Circular HSC (1999) 177

Seftel, A. (2007) Testosterone replacement therapy for male hypogonadism: part III. Pharmacologic and clinical profiles, monitoring, safety issues, and potential future agents. *Int J Impot Res*, **19**:2-24

Sherwin, B. B. (2002) Randomized clinical trials of combined estrogen-androgen preparations: effects on sexual functioning. *Fertil Steril*, **77 (Suppl 4)**:S49-S54

Sneader, W. (2005) Drug discovery – a history. *John Wiley & Sons Ltd, Chichester*, **pp 135-136**

Taylor, M.J., Rudkin, L., Hawton, K. (2005) Strategies for managing antidepressant-induced sexual dysfunction: systematic review of randomised controlled trials. *J Affect Disord*, **88**:241-254

Thase, M.E., Haight, B.R., Richard, N.et al (2005) Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *J Clin Psychiatry*, **66:**974-981

Werneke, U., Northy, S., Bhugra, D. (2006) Antidepressants and sexual dysfunction. *Acta Psych Scand*, **114**:384-397

Werneke, U., Turner, T. and Priebe, S. (2006) Complementary alternative medicine in psychiatry: a review of effectiveness and safety. *Br J Psych*, **188**:109-121

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