Choosing between different antidepressants

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Disclosures

- I have an interest in relation to one or more organisations that could be perceived as a possible conflict of interest in the context of the subject of this presentation. The relationships are summarised below:

Interest	Name of organisation
Consultancy fees	2014 and earlier: none 2015: Galen Limited; Sunovion Pharmaceuticals Europe Ltd; myTomorrows; Cyberonics Europe BVBA 2016, 2017: none
Speaker fees	None
Research support	None

- I do not hold any shares in, nor have any ongoing financial relationship with, any pharmaceutical or biomedical company

Choosing an antidepressant

- Match the antidepressant to the individual patient as far as possible, by joint decision
  - Efficacy
  - Tolerability
  - Special considerations?

Choosing an antidepressant: drug class

- TCAs vs SSRIs

Anderson IM, 2000. J Affect Disord 58(1):19-36

- MAOIs vs TCAs

Thase ME et al, 1995. Neuropsychopharmacology 12(3): 185-219

- RIMAs vs TCAs, SSRIs, classical MAOIs

Lotufo-Neto F et al, 1999. Neuropsychopharmacology 20(3):226-47

- SSRIs vs dual-acting (5-HT+NA)

Papakostas GI et al, 2007. Biol Psychiatry 62(11):1217-27

- SSRI vs NARI

Uher R et al, 2009. Br J Psychiatry 194:252-259

No class is more or less effective than any another to a clinically significant extent

Choosing an antidepressant: drug class

- No overall class differences in efficacy, but
  - Small signal for superiority of **amitriptyline** over SSRIs
  - Classical MAOIs (but not RIMAs) better than TCAs for *atypical* depression
  - Very small signal for superiority of **venlafaxine** over other dual-acting drugs
  - NARI > SSRI for biological symptoms
  - SSRI > NARI for cognitive symptoms

Network meta-analysis of efficacy and dropouts

Cipriani A et al, 2009. Lancet 373(9665):746-58

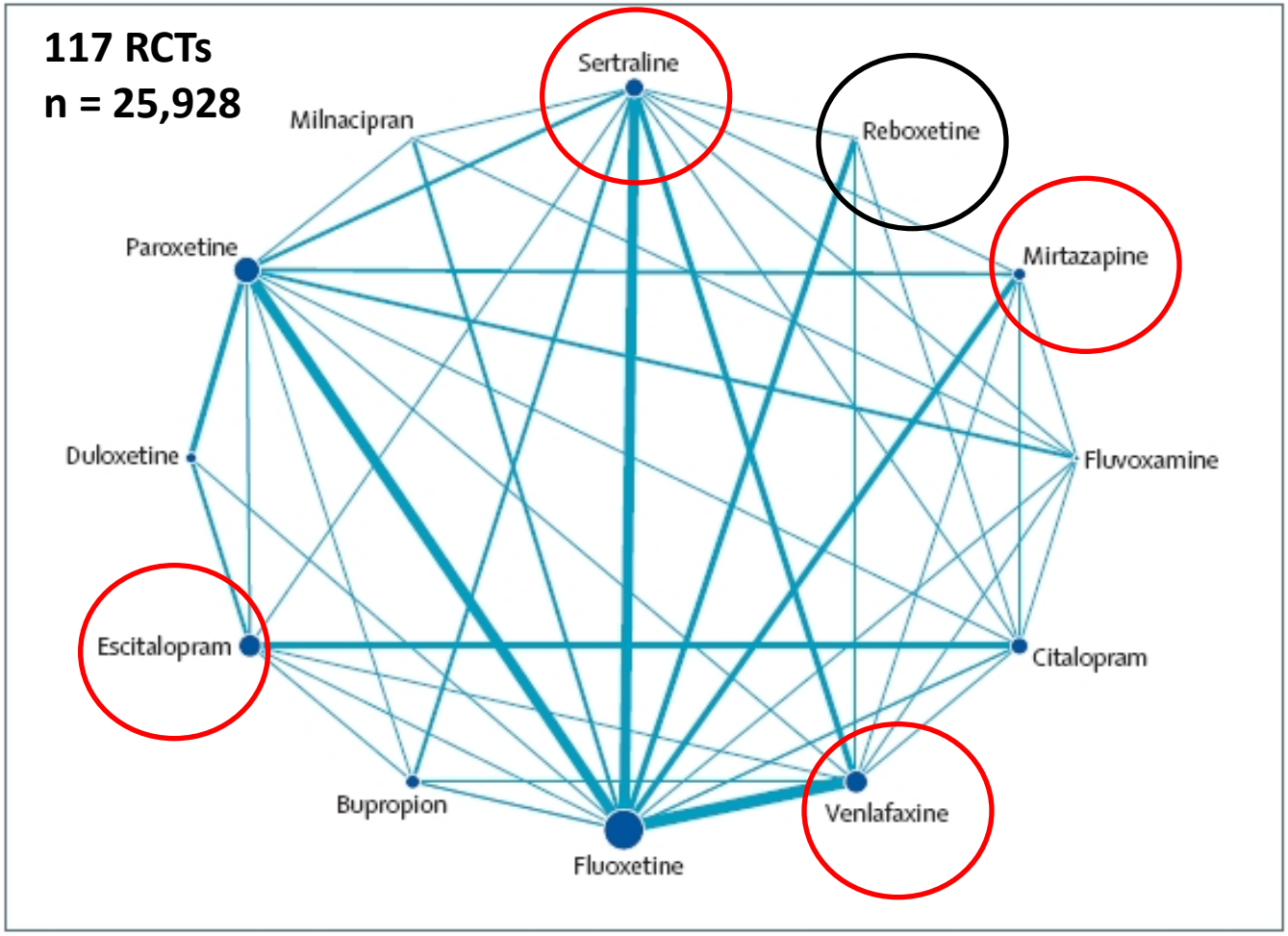


Figure 2: **Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)** The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size). The network of eligible comparisons for acceptability (dropout rate) analysis is similar.

Superior antidepressants?

Montgomery SA et al, 2007. Int Clin Psychopharmacol. 22(6):323-9

- Superiority over other ADs (at least 2 head to head good RCTs) :
  - Definite: clomipramine (150mg), venlafaxine (particularly ≥200mg), escitalopram (20mg) NB: also Cipriani et al, 2009 for VNFX and ESCITAL
  - Probable: milnacipran (SNRI, 100mg), duloxetine (80 not 60mg), mirtazapine (24-72mg)
- Superiority in severe depression:
  - Definite: escitalopram
  - Probable: venlafaxine
  - Possible: milnacipran and clomipramine
- **Escitalopram:**
  - Superiority over other SSRIs, duloxetine, and venlafaxine (severe depression) (Montgomery & Möller, 2009. Int Clin Psychopharmacol. 24(3):111-8; Cipriani A et al, 2009. Cochrane Syst Rev CD006532)
  - Evidence for dose-response (Gorman JM et al, 2002. CNS Spectrum 7:40-4)

Superior antidepressants?

- Differences between individual drugs are relatively modest
- Some evidence for superiority of clomipramine, venlafaxine (⩾200 mg), escitalopram 20 mg, sertraline, amitriptyline, mirtazapine
- Differences in tolerability are much greater

Network meta-analysis of efficacy and dropouts

Cipriani A et al, 2009. Lancet 373(9665):746-58

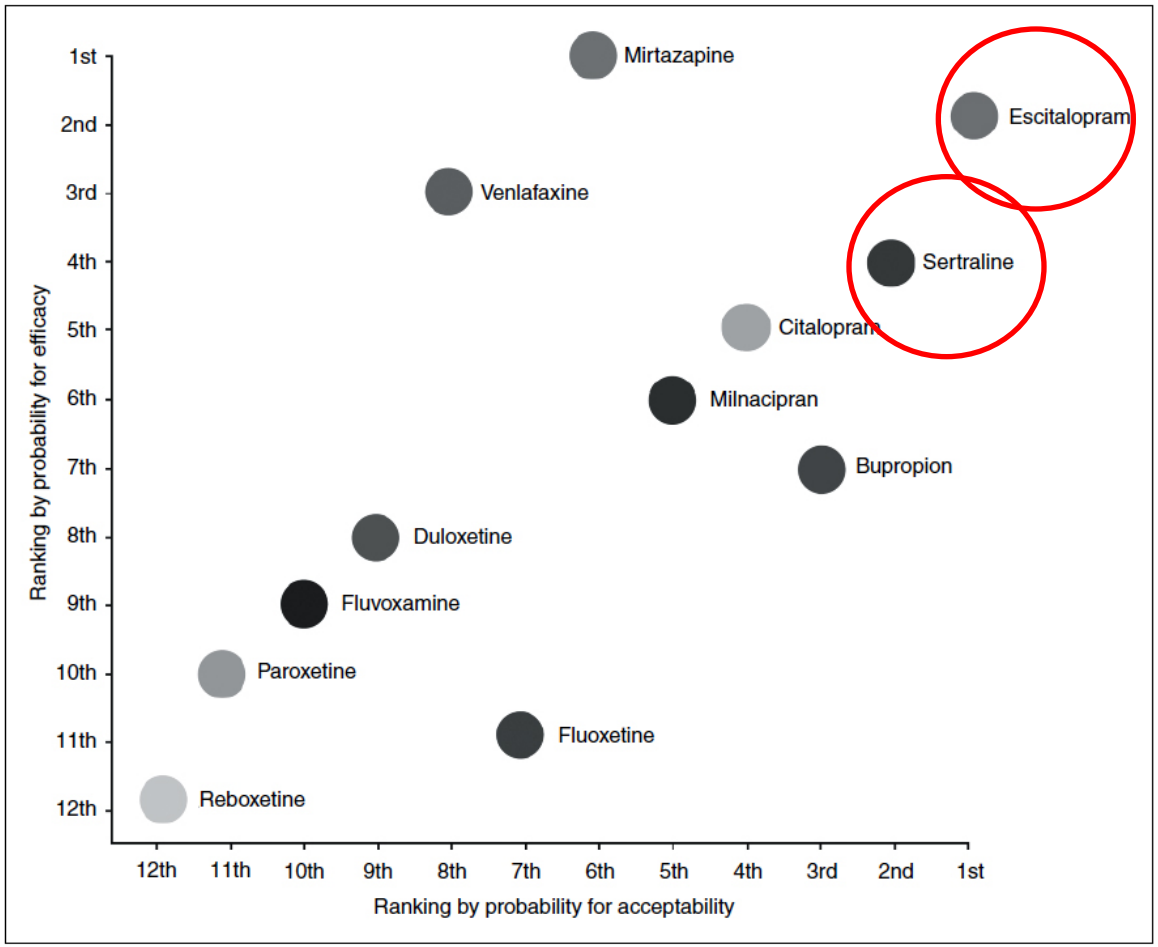


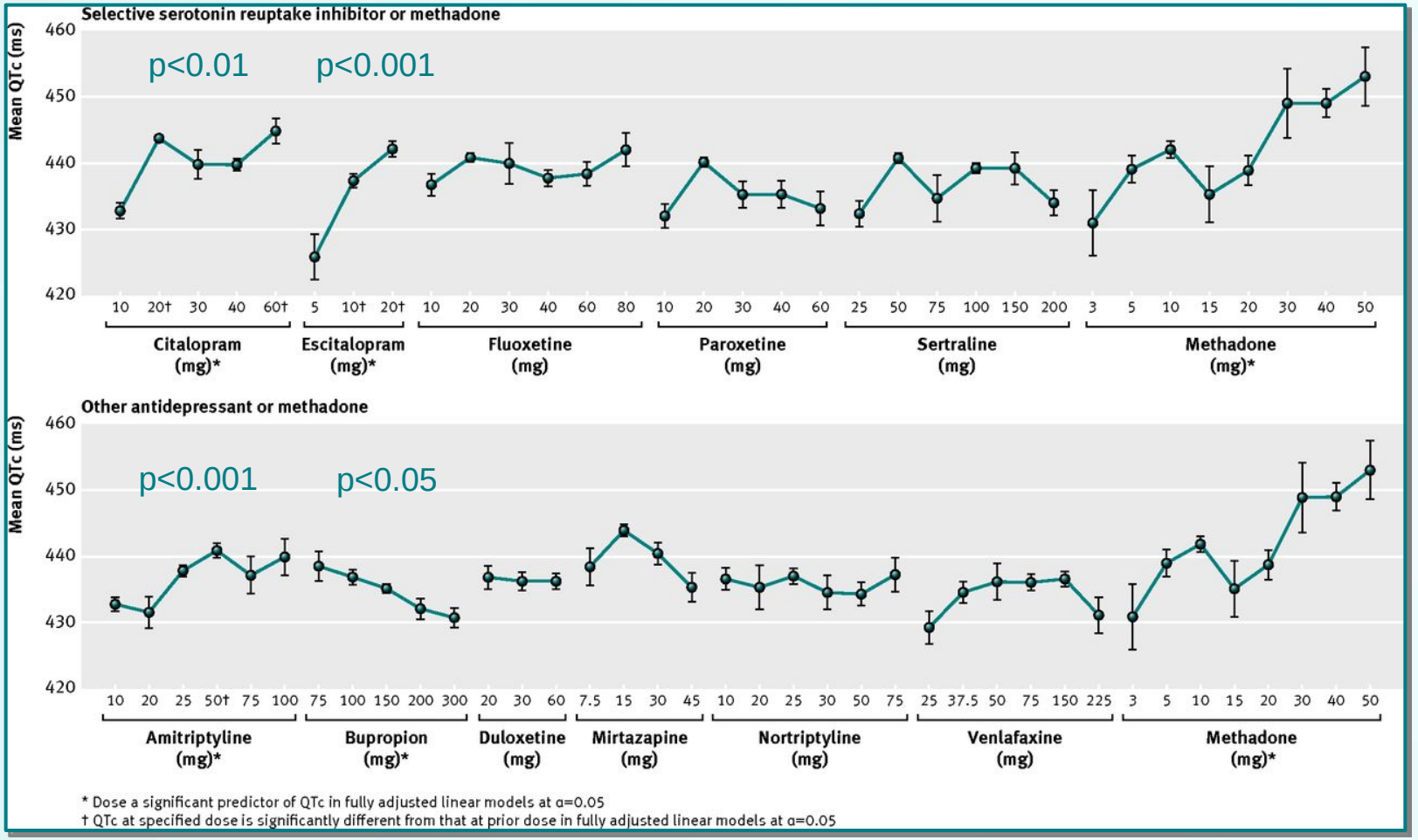
Figure 1. Rankings of antidepressants according to relative efficacy and acceptability. The graph is drawn from the data for cumulative probabilities of each antidepressant being placed in the top four treatments for efficacy and acceptability in Cipriani et al. (2009). Reproduced from Cipriani A, Furukawa TA, Salanti G, et al (2009). Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *The Lancet* 373:746–758 with permission from Elsevier.

Nutt DJ, 2009. J Psychopharm 23(8): 865–6

Mean (SD) QTc interval recorded on ECG 14–90 days after prescription of antidepressant or methadone, by drug dose

Castro V M et al. BMJ 2013;346:f288

38,397 adult patients from New England with ECG recorded after prescription of AD or methadone 1990-2011



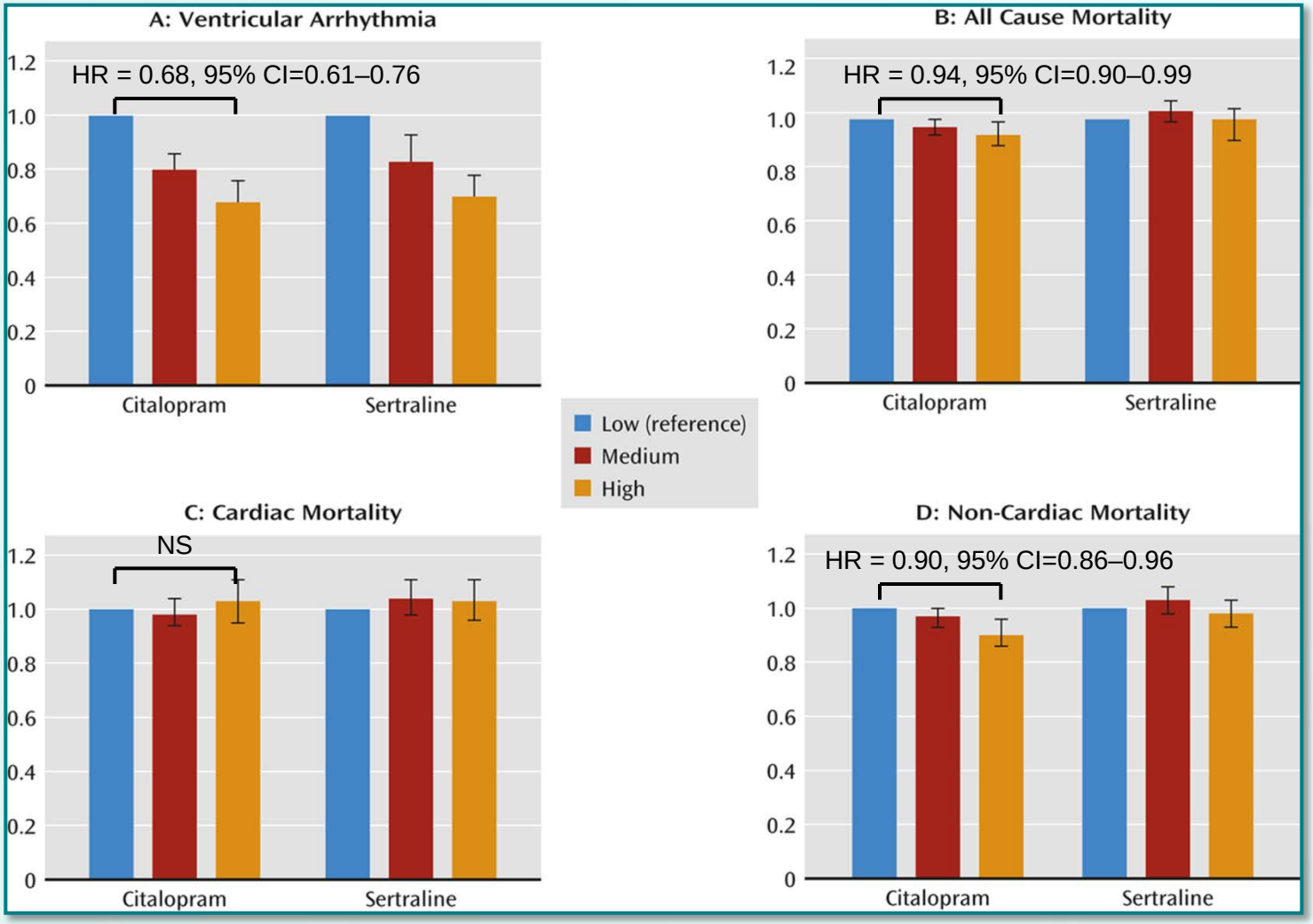
- modest prolongation of QT interval with citalopram, escitalopram and amitriptyline
- 13.1% of patients who started CIT with QTc in the normal range shifted to "abnormal" (M: ≥451ms; F: ≥471) after dose increase

Clinical implications of QTc prolongation

- QTc prolongation associated with torsade de pointes (TdP).
  - QTc normally around 400ms with upper limit of 460ms in women and 450ms in men. 500ms is considered a major risk factor for TdP.
  - However usually TdP only occurs if other risk factors
    - Age over 65
    - Female
    - Myocardial hypertrophy (e.g. secondary to hypertension)
    - Congenital QT prolongation
    - Bradycardia
    - Electrolyte disturbance (hypokalaemia or hypomagnesemia)
    - Co-administration with a second drug increasing QTc
    - High levels of the drug which may be due e.g. to:
      - Overdose
      - Inhibition of metabolism by other medication or CYP450 status
      - Hepatic or renal failure leading to decreased clearance

Clinical and mortality outcomes of patients treated with citalopram and sertraline

Zivin K et al, 2013. Am J Psychiatry 170(6):642-50



Low dose
- citalopram ≤20 mg/day
- sertraline 1–50 mg/day

Medium dose
- citalopram 21-40 mg/day
- sertraline 50-100 mg/day

High dose
- citalopram >40 mg/day
- sertraline >100 mg/day

n=618,450 treated between 2004 and 2009

- Higher doses of CIT associated with *lower or non-increased* risk

So what to do…?

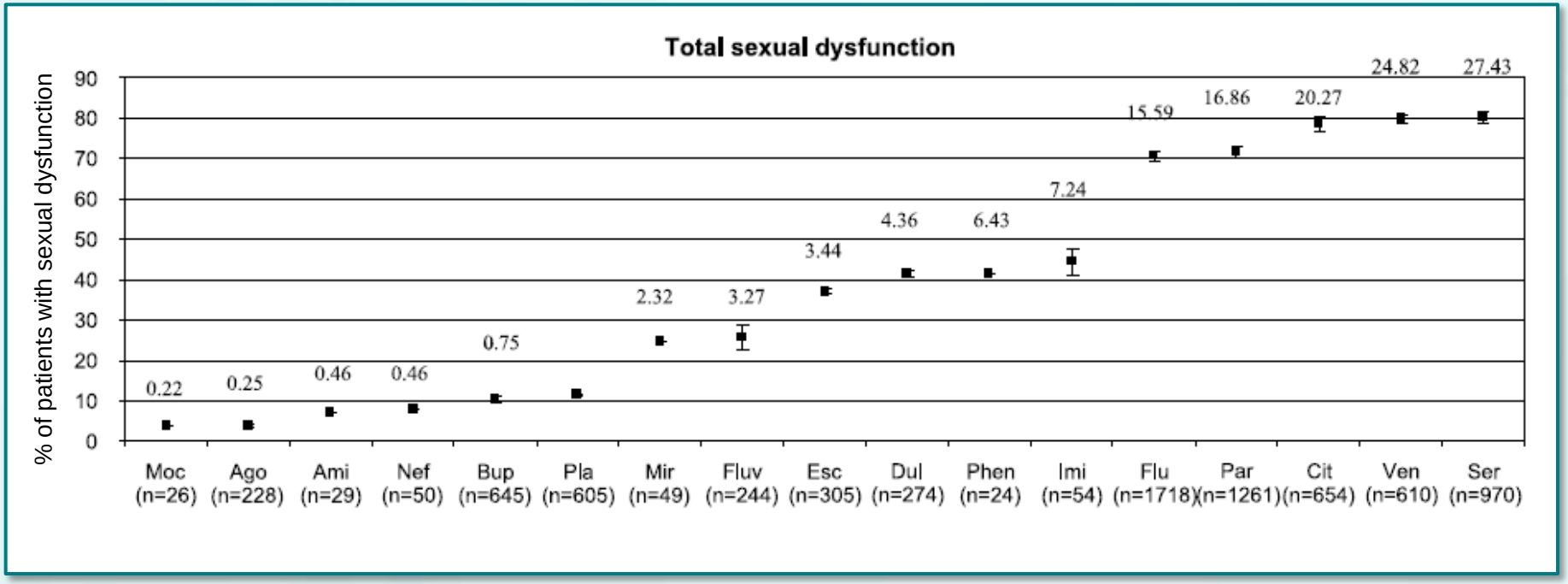
Things to consider:

- Does the patient have any risk factors for TdP?
- Has the patient demonstrated response to citalopram or escitalopram?
  - At what dose?
- If doing anything outwith MHRA guidance this should always be discussed with the patient and recorded in the notes
  - Especially in such circumstances consider doing an ECG with any change in medication (that is all the treatments a patient is on)
    - If QTc > 500ms then probably needed to adjust medication
    - If QTc < 480ms then probably OK, but monitor

Sexual dysfunction associated with antidepressants

Serretti A & Chiesa A, 2009. J Clin Psychopharmacol 29:259-66

Meta analysis of antidepressant trials which included a direct measure of sexual function (direct question or rating scale). Studies including patients that had a primary sexual dysfunction were excluded.



Mean total sexual dysfunction with placebo was 14.2%. The absolute % values and odds ratios vs. placebo are reported for each antidepressant.

Ago indicates agomelatine; **Ami**, amineptine; **Bup**, bupropion; **Cit**, citalopram; **Clo**, clomipramine; **Dul**, duloxetine; **Esc**, escitalopram; **Flu**, fluoxetine; **Fluv**, fluvoxamine; **Im**, imipramine; **Mr**, mirtazapine; **Moc**, moclobemide; **Nef**, nefazodone; **Par**, paroxetine; **Phe**, phenelzine; **Pla**, placebo; **Sel**, selegiline; **Ser**, sertraline; **Ven**, venlafaxine

AD discontinuation (withdrawal) syndrome

Haddad PM & Anderson IM, 2007. Advances in Psychiatric Treatment 13(6):447-57

- Common symptoms:
  - dizziness
  - headache
  - nausea
  - lethargy
- Rarer:
  - ataxia
  - electric shocks
  - EPSE
  - hypomania/mania
- Plenty of scope for misdiagnosis!

- Characteristics:
  - Abrupt onset
  - Usually short-lived (but can last weeks)
  - Rapid resolution when AD reinstated
- Classes:
  - All AD classes:
    - TCA, SSRIs, SNRIs, MAOIs, mirtazapine, nefazodone
    - Most often seen these days with **venlafaxine** and **paroxetine**

Antidepressant-induced sweating

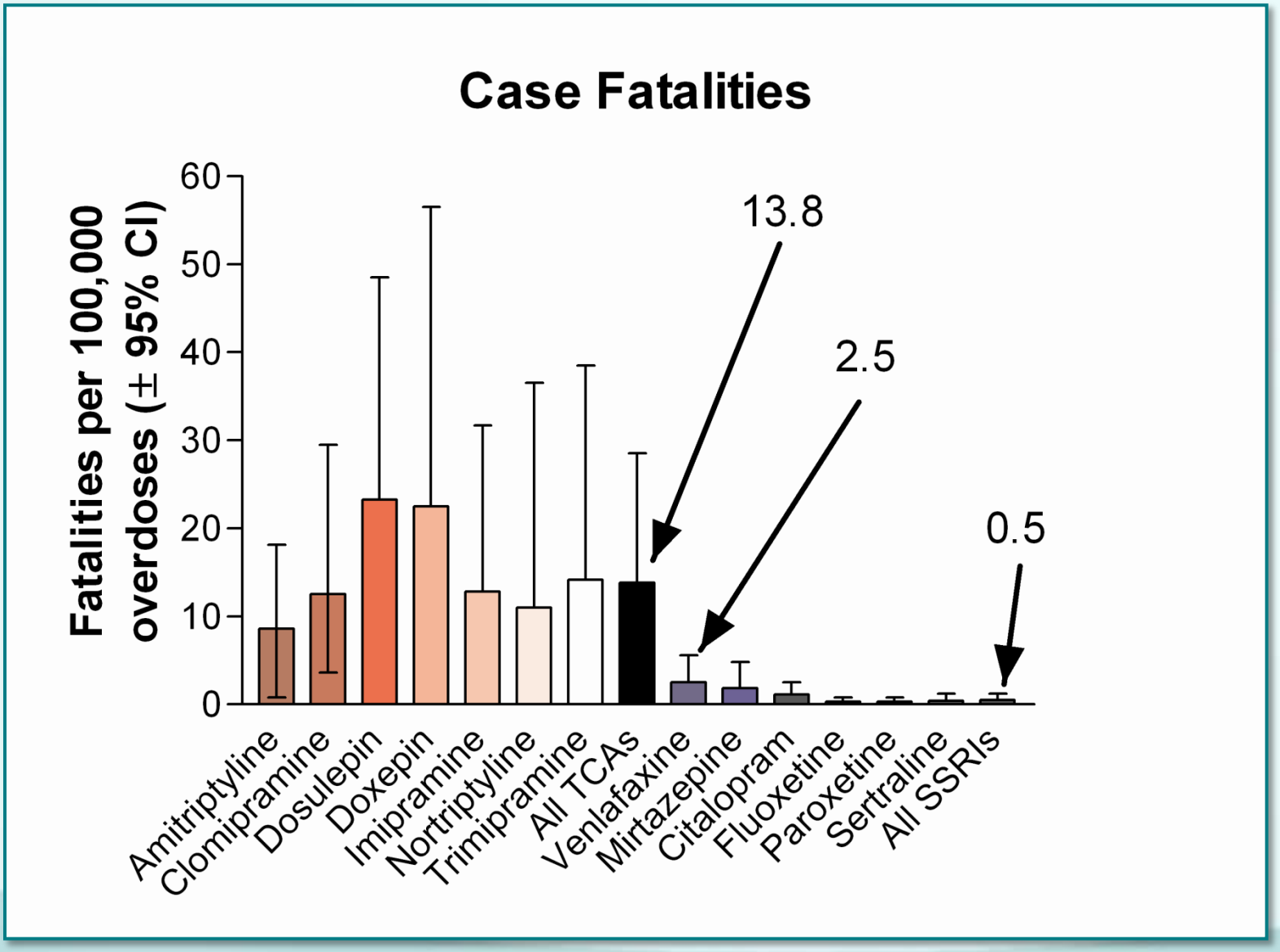
- Also known as diaphoresis; antidepressant-induced excessive sweating (AIES)
- Mainly scalp, face, neck, chest
- 10% of patients on SSRIs, 14% on TCAs (Trindade E et al, 1998. CMAJ 159:1245-52)
- Drugs which increase 5-HT and/or NA

Drug	Incidence of AIES (%)
Bupropion	22.3
Venlafaxine XL	14
Citalopram	11
Paroxetine	9-14
Sertraline	5-8
Escitalopram	4-8
Fluoxetine	8
Trazodone	1.4

Marcy TR & Britton ML, 2005. Ann Psychopharmacol 39:748-52

Case fatalities for antidepressants

Hawton K et al, 2010. B J Psych 196(5):354-8



International Journal of Neuropsychopharmacology (2007), **10**, 661–673. Copyright © 2007 CINP
doi:10.1017/S1461145707007766

Efficacy of agomelatine, a MT_1/MT_2 receptor agonist with 5-HT_{2C} antagonistic properties, in major depressive disorder

Jean Pierre Olié[1] and Siegfried Kasper[2]

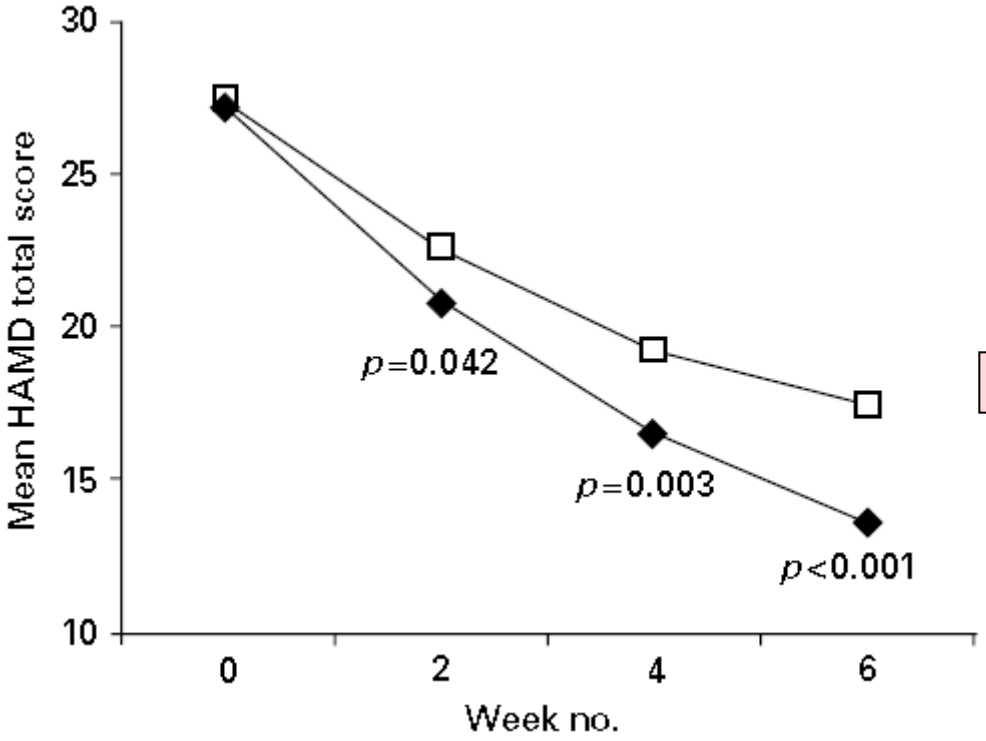


Table 3. Adverse events occurring in ⩾2% of patients in any treatment group

Adverse event	Number of patients (%)		
	Agomelatine ($n=118$)	Placebo ($n=120$)	p value for the difference[a]
Headache	6 (5.1)	17 (14.2)	0.027
Fatigue	6 (5.1)	2 (1.7)	0.170
Nausea	5 (4.2)	6 (5.0)	1.000
Dizziness	5 (4.2)	5 (4.2)	1.000
Nasopharyngitis	4 (3.4)	7 (5.8)	0.539
Influenza	3 (2.5)	4 (3.3)	1.000
Dry mouth	3 (2.5)	1 (0.8)	0.368
Nightmare	0 (0.0)	4 (3.3)	0.122

Agomelatine 25-50 mg n = 116; placebo n = 119
Repeated measures ANOVA

Agomelatine – effective?

Agomelatine:

- Publication bias evident. Critical review including unpublished (EMA, FDA, Novartis) data: "does not have clinically significant advantages compared with other ADs ... should only be considered as an alternative drug for patients who do not respond to or cannot tolerate other ADs" (Howland RH, 2011. Drug Safety 34(9):709-31)
- Liver function tests should be performed for all doses at initiation of treatment, at around week 3, 6, 12 and 24 weeks and thereafter where clinically indicated
- Agomelatine is contraindicated in patients with hepatic impairment (i.e. cirrhosis or active liver disease)

Vortioxetine: safety and tolerability

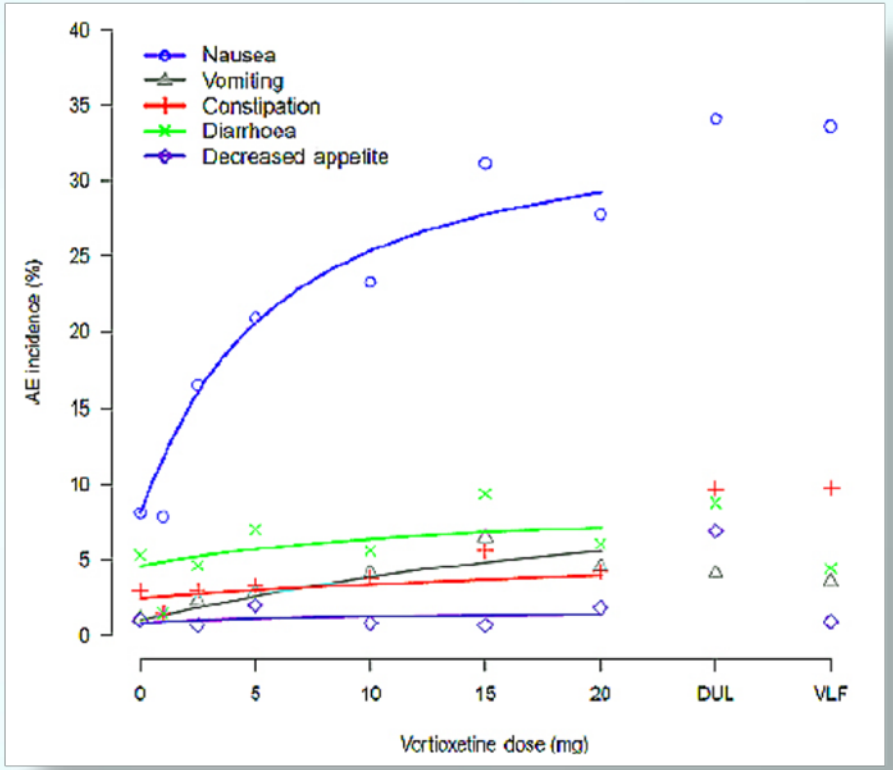
Baldwin DS et al, 2016. J Psychopharmacol 30(3):242-52

Safety and tolerability assessed (5-20mg)

- Short-term (6-8 w) RCTs vs placebo (n=3018)
- Long-term (up to 52 w) open-label (n=2457)
- Six studies included VEN 225mg or DUL 60mg as active reference

Most common adverse events

- Dose-dependent nausea and vomiting, particularly **nausea**
  - Generally mild to moderate
  - Plateaued at 15mg
  - Mainly in first 2 weeks
  - Transient: median duration 9-16 days



Vortioxetine: safety and tolerability

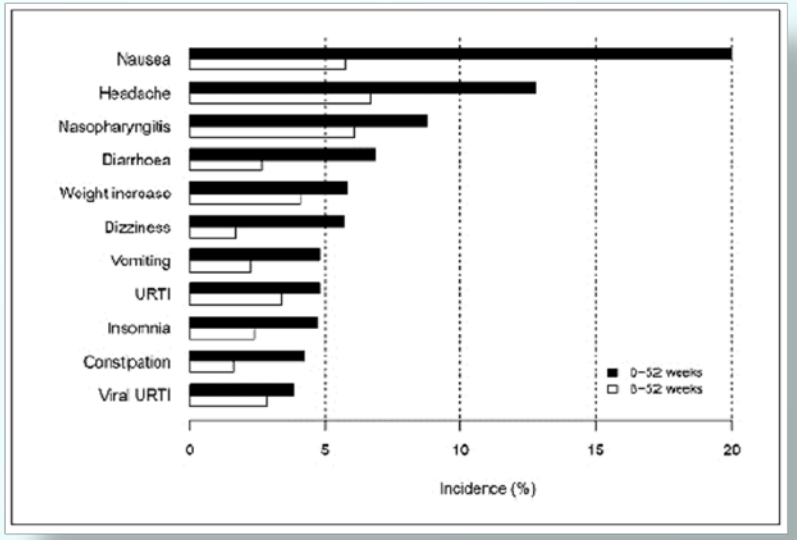
Baldwin DS et al, 2016. J Psychopharmacol 30(3):242-52

Placebo level:

- Headache, dry mouth, dizziness, constipation, insomnia, somnolence, fatigue, sleep disruption, hyperhidrosis
- Discontinuation symptoms
  - $t_{1/2}$ = 66hr
- Akathisia, restlessness
- Sexual dysfunction (5, 10, 15mg)
  - 5-HT_{1A} agonist
- Suicide-related events
- Weight gain
- Cardiovascular parameters, including QTc interval

Long-term studies

- Mean weight change
- 0.8kg (5-10mg) 0.5kg (15-20mg)
- Low rate of newly emerging AEs



"vortioxetine 5-20mg/day is 5.1 times more likely to result in a therapeutic response than a discontinuation due to a treatment-emergent adverse event"

Citrone L, 2016

Factors to consider in choosing an antidepressant

- patient preference (B)
- associated psychiatric disorder that may specifically respond to a particular class of antidepressant (e.g. OCD and SRIs) (B)
- previous treatment response to a particular drug (D)
- tolerability and adverse effects of a previously given drug (D)
- likely side effects (e.g. sedation, sexual dysfunction, wt gain) (C)
- low lethality in overdose if history or likelihood of overdose (D)
- concurrent medical illness or condition that may make the antidepressant more noxious or less well tolerated (C)
- concurrent medication that may interact (C)
- a family history of differential antidepressant response if choosing between a TCA and MAOI (C)
- atypical features (phenelzine better than imipramine) (B)

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Antidepressant side effect profiles

BAP Depression Guidelines, 2015 Table 5

Table 5. Side-effect profiles and lethality in overdose of commonly used antidepressant drugs.

Drug	Action	Side effect								Inhibition of hepatic enzymes	Lethality in overdose
		Anti-cholinergic[a]	Sedation	Insomnia/ agitation	Postural hypotension	Nausea/ gastro intestinal	Sexual dysfunction	Weight gain	Specific adverse effects		
Tricyclic antidepressants											
clomipramine	SRI+NRI	++	++	+	++	+	++	+		–	moderate
amitriptyline, dosulepin	NRI>SRI	++	++	–	++	–	+	++		–	high
imipramine	NRI>SRI	++	+	+	++	–	+	+		–	high
desipramine, nortriptyline	NRI	+	+	+	+	–	+	–		–	high
lofepramine	NRI	+	–	+	+	–	?	–	sweating	–	low
Selective serotonin reuptake inhibitors											
citalopram, sertraline	SRI	–	–	+	–	++	++	–		–	low
fluoxetine, fluvoxamine, paroxetine	SRI	–	–	+	–	++	++	–		++	low
Other reuptake inhibitors											
maprotiline	NRI	++	++	–	–	–	+	++	increased seizure potential	?	high
reboxetine	NRI	+	–	+	–	–	+	–		–	low
venlafaxine	SRI>NRI	–	–	+	–	++	++	–	hypertension, sweating	+	moderate
duloxetine	SRI+NRI	–	–	+	–	++	++	–		–	?low
bupropion[b]	?DRI+NRI	–	–	+	–	–	–	–	increased seizure potential	–	? moderate
Receptor antagonists											
trazodone	$5\text{-HT}_2 + \alpha_1 > \text{SRI}$	–	++	–	++	–	–	+	priapism	?	low
nefazodone	$5\text{-HT}_2 > \text{SRI}$	+	+	–	+	+	–	++		++	low
mianserin	$5\text{-HT}_2 + \alpha_1 + \alpha_2$	+	++	–	–	–	–	–		?	low
mirtazapine	$5\text{-HT}_2 + 5\text{-HT}_3 + \alpha_2$	–	++	–	–	–	–	++		–	low

(Continued)

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Antidepressant side effect profiles

BAP Depression Guidelines, 2015 Table 5

Table 5. (Continued)

Drug	Action	Side effect								Inhibition of hepatic enzymes	Lethality in overdose
		Anti-cholinergic[a]	Sedation	Insomnia/ agitation	Postural hypotension	Nausea/ gastro intestinal	Sexual dysfunction	Weight gain	Specific adverse effects		
Monoamine oxidase inhibitors											
phenelzine, tranylcypromine, isocarboxazid	Irreversible	+	+	++	++	+	++	++	hypertensive crisis with sympatheto-mimetics, oedema	?	high
moclobemide	RIMA	–	–	+	–	+	–	–		–	low
Other											
agomelatine	M + 5-HT_{2C}	–	+	+	–	+	–	–	Requires LFT monitoring	–	?
vortioxetine	SRI + 5-HT_3 + 5-HT_7 + 5-HT_{1B} + 5-HT_{1A}	–	–	–	–	++	+/–	–		–	?

NRI: noradrenaline reuptake inhibitor; SRI: serotonin reuptake inhibitor; DRI: dopamine reuptake inhibitor; 5-HT_{1A}: 5-HT_{1A} agonist; 5-HT_{1B}: 5-HT_{1B} partial agonist; 5-HT_2/5-HT_{2C}: 5-HT_2/5-HT_{2C} antagonist; 5-HT_3: 5-HT_3 antagonist; 5-HT_7: 5-HT_7 antagonist; α_1/α_2: α_1 antagonist/α_2 antagonist; M: melatonin agonist; RIMA: Reversible inhibitor of monoamine oxidase-A.

++relatively common or strong.

+may occur or moderately strong.

-absent or rare/weak.

? unknown/insufficient information.

[a] These refer to symptoms commonly caused by muscarinic receptor blockade including dry mouth, sweating, blurred vision, constipation and urinary retention; however, the occurrence of one or more of these symptoms may be caused by other mechanisms and does not necessarily imply that the drug binds to muscarinic receptors.

[b] These are not licensed in the UK but are elsewhere in the world.

These side-effect profiles are not comprehensive, have been compiled from various sources and are for rough comparison only. Details of drugs used and potential cautions and interactions should be looked up ideally in the original SPCs, or in a suitable reference book such as the British National Formulary (Joint Formulary Committee, 2014).

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- atypical features (phenelzine better than imipramine) (B)

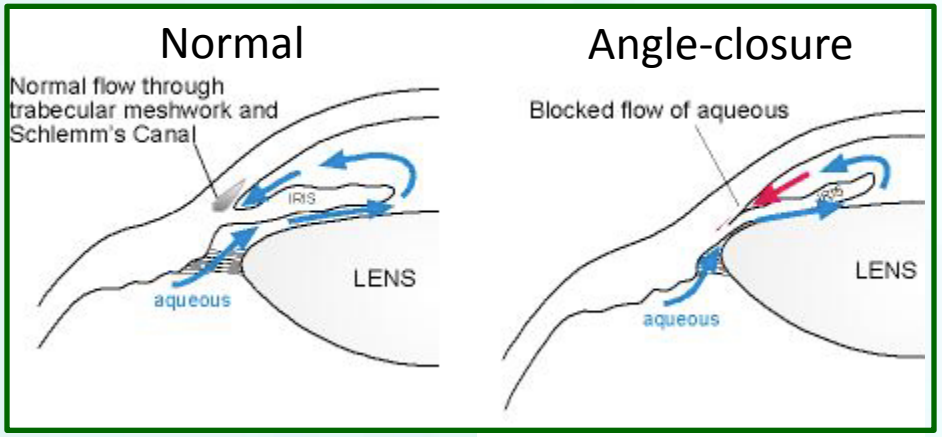
Special considerations in prescribing: comorbid illness

- Cardiovascular disease
  - Avoid TCAs in patients at high risk of CVS disease, arrhythmias and cardiac failure (C)
  - In acute coronary syndromes choose drugs which do not increase the risk of subsequent cardiac events (S):
    - there is best evidence for SSRIs (particularly sertraline), mirtazapine and bupropion
- Bleeding disorders
  - choose antidepressants that are not SRIs if possible (B)
  - In patients on aspirin/NSAIDs needing an antidepressant choose a non-SRI (A) or combine an SRI with an ulcer-protective drug (B)

Acute angle-closure glaucoma

- Acute angle-closure glaucoma (aka narrow-angle glaucoma) occurs in eyes with a narrow anterior chamber angle where aqueous fluid drainage is reduced or blocked → raised intraocular pressure
- Caused by drugs with higher *antimuscarinic* activity

Commonest in older age, East Asian and Inuit populations
Rarer in black people



Lower risk	Moderate risk	Higher risk
Agomelatine Bupropion MAOIs Moclobemide Trazodone Tryptophan	Duloxetine Venlafaxine Mirtazapine SSRIs	TCAs

Symptoms

- Pain in eye and orbit, even frontal or generalised headache
- Red eye, hazy cornea, poorly reactive mid-dilated pupil
- Coloured haloes around lights
- Blurred vision → rapidly to visual loss
- Nausea and vomiting

Treatment

- Stop antidepressant
- Refer immediately - day or night! Patients need urgent treatment in order to save sight.

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Factors to consider in choosing an antidepressant

- In more severely ill patients, and where maximising efficacy is of overriding importance, consider these in preference to other ADs:
  - clomipramine (B), venlafaxine (⩾150 mg) (B), escitalopram (20 mg) (B), sertraline (B), amitriptyline (C), or mirtazapine (C)

Conclusion

- Match the antidepressant to the individual patient as far as possible, by joint decision
  - Efficacy – differences are rather small
  - Tolerability – anticipated side effects likely to be main factor in choice
  - Special considerations? Don't forget full medical history and list of all current drugs