South African National Essential Medicine List
Primary Level and Adult Hospital Level Medication Review Process
Component: Mental Healthcare conditions

1. Executive Summary

Date: 10 October 2017
Medicine (INN): Review of SSRIs – Recommended: fluoxetine and sertraline or escitalopram
Medicine (ATC): NO6AB
Indication (ICD10 code): Depression or anxiety disorders (F32.0 – F32.9; F33.0 – F33.9; F41.0 – F41.9)
Patient population: Adults, adolescents, elderly, PLWHA
Level of Care: Primary level of care
Prescriber Level: Nurse Prescriber, Doctor
NNT: n/a
Current standard of Care: Fluoxetine / citalopram / amitryptiline
Motivator/reviewer name(s): Dr Lesley Robertson, Dr Renee de Waal assisted with appendix II.
PTC affiliation: Gauteng Provincial PTC

2. Name of author(s)/motivator(s)

Dr Lesley Robertson, Dr Renee de Waal assisted with appendix II.

3. Author affiliation and conflict of interest details

- Dr Lesley Robertson
  Affiliated to the University of the Witwatersrand and the South African Society of Psychiatrists; Co-opted to support PHC Committee (2016-2018).
  Conflicts of interest: Dr Reddy Laboratories annual sponsorship of Public Sector Psychiatry Forum (SASOP); Honorarium from Sanofi Aventis (2015) channelled to South African Society of Mental Health and Deafness via SASOP.

Note: Dr Robertson was recused from the decision-making process regarding a recommendation.

- Dr Renee de Waal
  Affiliated to the University of Cape Town; Chairperson of PHC Committee (2016-2018).
  Conflicts of interest: None.

4. Introduction/Background

A review of SSRIs to ascertain which have the best evidence for efficacy and tolerability.

5. Purpose/Objective

- **P:** Patients with depression or anxiety disorders
- **I**: Any SSRI
- **C**: Placebo /Alternative antidepressant
- **O**: Reduction in depressive or anxiety symptomatology

6. Methods

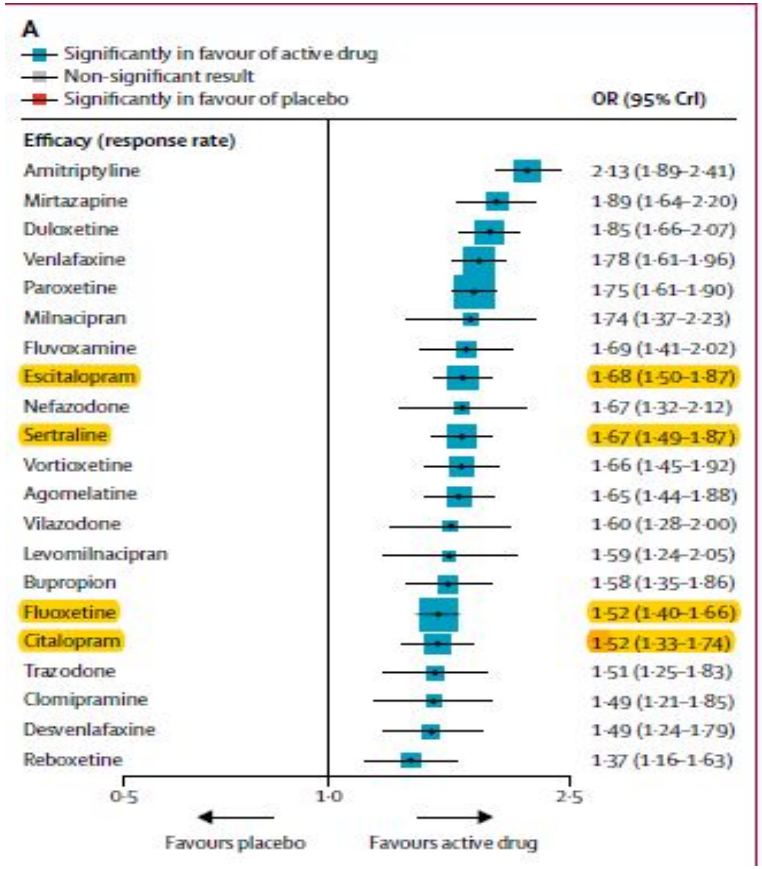
Search strategy:

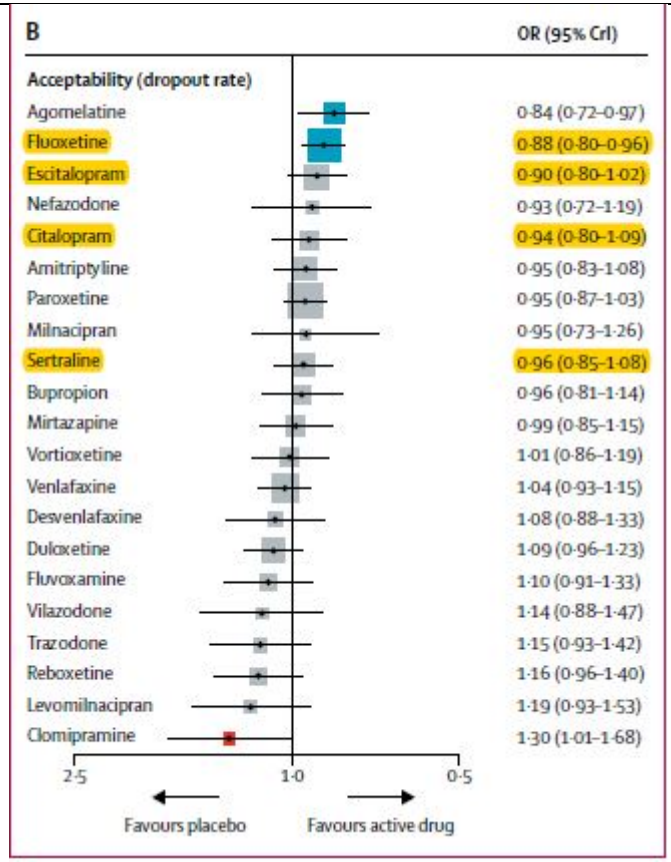
Pubmed was searched on 02/10/2017 using the terms “antidepressants and depression or anxiety” and articles were restricted to meta-analyses published between 06/10/2007 and 02/10/2017. A total of 588 titles were retrieved (list attached) of which 529 were rejected as not relevant or not a meta-analysis.
From 59 abstracts, which were screened for analyses with evidence of comparison between the different antidepressants, 13 articles were selected. A search of the Cochrane database yielded 4 articles and an additional citation search yielded 4 more articles. One of the Cochrane articles (Cipriani et al 2010 replaced Cipriani et al 2008 as both were of sertraline vs other antidepressants)

As no articles relevant to PLWHA had been identified a second Pubmed search was performed on 03/10/2017 with the term “antidepressants and HIV” for systematic reviews with no date limits.43 titles were retrieved, of which 38 were rejected as not relevant. Of the 5 abstracts, 4 articles were selected as possibly indicating differences between antidepressants.

Excluded study:
The list for excluded studies and reasons for exclusion are attached as Appendix I.

Evidence synthesis and quality:

Studies of efficacy ±tolerability / safety				
Disorder / Patient population	**Author**	**Study design**	**Outcome measure**	**Results / Effect Size**
Depression – acute treatment	**Cipriani et al. (2018)[1]** High quality	**Network Meta-analysis** Included data *only for drugs in the therapeutic range,* therefore escitalopram and citalopram compared according to therapeutic doses. Used 8 weeks as time point for outcome measures Excluded trials with >20% of participants with bipolar, psychotic or treatment resistant depression, or with serious concomitant medical illness 522 RCTs included	**Primary outcomes** - Efficacy: >50% reduction in depression score - Acceptability: All-cause discontinuation.	

				
Depression – acute treatment	Magni et al. (2013)[2] High quality	Cochrane Review of **Fluoxetine** vs other antidepressants 171 RCTs, N=24 868 For outcome of failure to respond: Vs Citalopram 1 trial, N=59 Vs Escitalopram 1 trial, N=240 Vs Mirtazepine 4 trials, N=600 Vs Sertraline 6 trials, N=1188 Vs Venlafaxine 12 trials, N=3387	**Failure to respond** (to achieve > 50% reduction on Hamilton Depression Scale - HDRS) was used, therefore an OR < 1 favours fluoxetine and > 1 the comparative medication **Tolerability:** Drop outs due to adverse effects (OR < 1 favours fluoxetine)	**Failure to respond:** Fluoxetine vs venlafaxine: OR 1.29 (95% CI 1.10 to 1.51) Fluoxetine vs sertraline: OR 1.37 (95% CI 1.08 to 1.74) Fluoxetine vs mirtazapine: OR 1.46 (95% CI 1.04 to 2.04) Fluoxetine vs citalopram: NS [OR 0.60 (95% CI 0.2 to 1.79)] Fluoxetine vs escitalopram: NS [OR 1.02 (95% CI 0.56 to 1.85)] **Tolerability (dropouts due to adverse effects):** Fluoxetine vs venlafaxine: OR 0.72 (95% CI 0.56 to 0.94)

				No significant difference between fluoxetine & citalopram, escitalopram, sertraline or mirtazapine
Depression – acute treatment	Cipriani et al. (2012)[3]	Cochrane Review of **Citalopram** vs other antidepressants 37 RCTs Vs Fluoxetine: 2 trials, N=673 Vs Escitalopram: 6 trials, N=1806 Vs Sertraline: 3 trials, N=551 Vs venlafaxine: 1 trial, N=151	**Failure to respond** (to achieve > 50% reduction on HDRS) was used, therefore an OR < 1 favours citalopram and > 1 the comparative medication **Tolerability:** Drop outs due to adverse effects	**Failure to respond:** Citalopram vs escitalopram: OR 1.47 (95% CI 1.08 to 2.02) Citalopram vs fluoxetine: NS [OR 1.03 [95% CI 0.75 to1.43] Citalopram vs sertraline: NS [OR0.53 (95% CI 0.20 to1.42)] Citalopram vs venlafaxine: NS [0.91 (95% CI 0.46 to1.78)] **Tolerability (drop-outs due to adverse effects):** No significant difference between citalopram & fluoxetine, escitalopram, sertraline or venlafaxine
Depression – acute treatment	Cipriani et al. (2009)[4]	Cochrane Review of **Escitalopram** vs other antidepressants 22 trials Vs Citalopram: 6 trials, N=1823 Vs Fluoxetine, 3 trials, N=783 Vs Sertraline, 2 trials, N=489	**Failure to respond** (to achieve > 50% reduction on HDRS) was used, therefore an OR < 1 favours escitalopram and > 1 the comparative medication **Tolerability:** Drop outs due to adverse effects	**Failure to respond:** Escitalopram vs Citalopram: OR 0.67 (95% CI 0.50 to 0.89) Escitalopram vs fluoxetine: NS [OR 0.81 (95% CI 0.60 to 1.10)] Escitalopram vs sertraline: NS [OR 1.06 (95% CI 0.73 to 1.53)] Citalopram vs venlafaxine: NS [OR 0.86 (95% CI 0.53 to 1.39)] **Tolerability (drop-outs due to adverse effects):** No significant difference between citalopram & fluoxetine, escitalopram, sertraline or venlafaxine
Depression – acute treatment	Cipriani et al.(2010)[5] High quality	Cochrane Review of **Sertraline** vs other antidepressants 59 trials Vs Citalopram, 1 trial, N=400 Vs Escitalopram 2 trials, N=489 Vs Fluoxetine 8 trials, N=1352 Vs Venlafaxine 5 trials, N=611	**Failure to respond** (to achieve > 50% reduction on HDRS) was used, therefore an OR < 1 favours sertraline and > 1 the comparative medication **Tolerability:** Drop outs due to adverse effects	**Failure to respond at 6 – 12 weeks:** Sertraline vs fluoxetine: OR 0.73 95% CI [0.59 to 0.92] Sertraline vs citalopram: NS [OR 0.93 (95% CI 0.61 to 1.42)] Sertraline vs escitalopram: NS [OR0.94 (95% CI 0.65 to 1.37)] Sertraline vs venlafaxine: NS [OR1.07 (95% CI 0.74 to1.54)] **Acceptability:** No significant difference with any groups
Depression – acute treatment	Cipriani et al. (2009)[6] High quality	**Network meta-analysis** of 12 antidepressants 117 RCTs, N=25 928 Fluoxetine: 54 RCTS Sertraline: 27 RCTs	**Response** At least 50% reduction in depression scale scores or "much improved" or very much improved" at 6 – 12 weeks of Rx	**Efficacy – direct analysis:** Escitalopram vs citalopram: OR 1.47 (95% CI 1.15 to1.90) Sertraline vs fluoxetine: OR 1.42 (95% CI 1.13 to 1.78) Escitalopram vs fluoxetine: NS [OR 1.23 (95% CI 0.87 to 1.74)] Escitalopram vs sertraline: NS [OR 0.90 (95% CI 0.62 to 1.30)]

		Escitalopram = 19 RCTs		**Efficacy – multiple treatments analysis** Fluoxetine vs escitalopram (but only 2 out of 5 RCTs included): OR 0.76 (95% CI 0.65 to 0.89) Fluoxetine vs sertraline (8 RCTs): OR 0.80 (95% CI 0.69 to 0.93) **Cumulative probability of being amongst the four most efficacious:** mirtazepine 24.4%; escitalopram 23.7%; venlafaxine 22.3%; sertraline 20.3%; citalopram 3.4%; paroxetine 0.1%; fluoxetine 0.0% **Acceptability (according to drop-out rates)** No significant differences between ADs **Cumulative probability of being amongst the four most acceptable:** escitalopram 27.6%; sertraline 21.3%; citalopram 18.7%; mirtazapine 4.4%; fluoxetine 3.4%; venlafaxine 0.9%; paroxetine 0.2%
Depression – acute Rx	Wang et al. (2014)[7]	Meta-analysis of head to head paroxetine vs fluoxetine trials 17 RCTs with 3,110 participants	At least a 50% reduction in depression scale scores or significant improvement in the CGI at the conclusion of therapy.	At 6 weeks, paroxetine > fluoxetine OR: 0.74; $p < 0.05$ But at 12 weeks fluoxetine > paroxetine (OR: 1.25; $p < 0.05$
Depression – acute & long-term Rx	Katzman et al.(2007)[8]	Meta-analysis of paroxetine vs other agents 51 trials, ?number of participants	Included acute and long-term trails	Results inconclusive
Depression – maintenance treatment	Hansen et al. (2008)[9]	Meta-analysis of 24 trials, data not pooled.	Prevention of relapse and prevention of recurrence.	Confirms an advantage of continuation of treatment but could not distinguish between antidepressants and cautions against inferring differences from given results.
Depression – elderly patients	Thorlund et al. (2015)[10]	Network meta-analysis 15 trials; 4588 participants Fluoxetine: 5 trials; N=1581 Citalopram 2 trials; N=539 Sertraline: 1 trial; N=728 Escitalopram: 2 trials; N=782	**Efficacy:** 50% reduction in depression scores **Safety:** Dizziness, falls	**Efficacy (RR of Partial Response):** Sertraline vs placebo: RR 1.28 (95% CI 1.07 to 1.51) Paroxetine vs placebo: RR 1.48 (95% CI 1.27 to 1.75) Duloxetine vs placebo: RR 1.62 (95% CI 1.26 to 2.05) Citalopram vs placebo: NS [RR1.07 (95% CI 0.7 to 1.48)] Fluoxetine vs placebo: NS [RR1.08 (95% CI 0.94 to 1.24)] Escitalopram vs placebo: NS [RR1.19 (95% CI 0.99 to 1.41)] Venlafaxine vs placebo: NS [RR 1.21 (95% CI 0.88–1.57)]

		Paroxetine: 4 trials, N=1016 Duloxetine: 1 trial, N=311 Venlafaxine: 1 trial, N=300		**Safety: (RR of Dizziness)** Sertraline vs placebo: RR 1.10 (95% CI 0.65 to 1.83) Fluoxetine vs placebo: RR 1.31 (95% CI 0.89to 1.92). Citalopram vs placebo: RR 1.45 (95% CI 0.69to 2.99) Paroxetine vs placebo: RR 1.47 (95% CI 0.83to 2.61) Escitalopram vs placebo: RR 1.58 (95% CI 0.69to 4.10) Duloxetine vs placebo: RR 2.94 (95% CI 1.03to 8.37) Venlafaxine vs placebo RR 3.18 (95% CI 1.60to 6.03)
Depression - elderly	Seitz et al. (2010)[11]	Meta-analysis of head to head trials – pooled estimates 7 trials; N=1288	Outcomes according to trials	No significant difference between citalopram and alternative ADs (included tricyclics, mianserin, venlafaxine and reboxetine only).
Depression – children and adolescents	Tsapakis et al. (2008)[12]	Meta-analysis of RCTs in juvenile depression (people < 20 years)	**Response:** >50% reduction of symptoms	Response: All antidepressants vs placebo: RR 1.22 (95% CI 1.15 to 1.31) TCAs vs placebo: RR 1.15 (95% CI 0.98 to 1.34) SSRIs vs placebo: RR 1.23 (95% CI 1.14 to 1.33) Fluoxetine vs other SSRIs: RR 1.45 (95% CI 1.24 to 1.70) No significant effect of antidepressants in children under 10 years; are effective in 10 and over (RR 1.19 (95% CI 1.09 to 1.30)) and more strongly so in 16 years and over (RR 1.27 (95% CI 1.15 to 1.40))
Anxiety Disorders – panic, GAD and social anxiety disorder (SAD)	Bandelow et al. (2015)[13]	Meta-analysis of medication & psychotherapy RCTS – analysed pre-post effect sizes to get a hierarchy of Rx efficacy 234 RCTs in total; N=37 333 138 RCTs using medication, N=30411 Fluoxetine: 7 studies (4 in Panic Disorder and 3 in SAD) Escitalopram: 8 studies (1 in Panic, 5 in GAD and 1 in SAD) Sertraline; 9 studies (3 in each disorder)	Outcomes – 50% reduction in relevant anxiety scale NB Study challenges NICE guidelines assertion that psychotherapy is as effective or superior to medication. Cohen's *d* - pre-post effect size	**For all anxiety disorders (Pre-Post effect size as Cohen's *d*)** SNRIs > Benzos > med +CBT > SSRIs > TCAs > Therapies > waitlist (drug studies all short term ≤ 14 weeks) All SSRIs except citalopram superior to placebo Quetiapine (3 studies; all in GAD): *d* 3.39 (95% CI 3.19 to 3.60) Escitalopram:*d* 2.75 (95% CI 2.09 to 3.41) Sertraline:*d* 2.23 (95% CI 1.56 to 2.90) Fluoxetine: *d* 1.69 (95% CI 1.16 to 2.22) Citalopram (2 studies): *d* 1.06 (95% CI 0.41 to 1.71) Fluvoxamine (12 studies): *d* 1.53 (95% CI 1.24 to 1.83) (Both citalopram studies on panic disorder. None on GAD or social anxiety disorder). SNRI - Venlafaxine (20 studies; 5 each in panic disorder & SAD, 10 in GAD): *d* 2.32 (95% CI 1.94 to 2.70)

Anxiety Disorders - GAD	Baldwin et al. (2011)[14]	Network probabilistic meta-analysis 46 RCTs in Syst Rev; 27 included in meta-analysis: Fluoxetine: 1 trial, N=90 Sertraline: 3 trials, N=749 Escitalopram: 5 trials, N=1652 Citalopram: No trials included	**Response:** 50% reduction in HAM-A score **Remission:** HAM-A score <7 **Tolerability:** Withdrawal due to AEs	**Response:** Placebo vs fluoxetine: OR 0.27 (95% CI 0.09 to 0.81) Placebo vs sertraline: OR 0.45 (95% CI 0.33 to 0.62) Placebo vs escitalopram: NS [OR 0.67(95% CI 0.39 to 1.14)] Escitalopram vs sertraline: NS [OR 0.68 (95% CI (0.29 to 1.59)] **Remission:** Placebo vs fluoxetine: OR 0.24 (95% CI 0.06 to 0.97) Placebo vs escitalopram: OR 0.34 (95% CI 0.20 to 0.57) Placebo vs sertraline: OR 0.78 95% CI (0.29 to 0.78) Escitalopram vs sertraline: NS [OR 1.43 (95% CI (0.52 to 3.84)] Escitalopram vs fluoxetine: NS [OR 0.62(95% CI 0.04 to 6.47) **Tolerability** (Odds of withdrawal due to adverse effects) Escitalopram vs placebo: OR 2.86 (95% CI 1.64 to 4.76) Sertraline vs placebo: NS [OR 1.12(95% CI 0.61 to 2.04)] Fluoxetine vs placebo: NS [OR1.54(95% CI 0.13 to 16.67)] Sertraline vs escitalopram: NS [0.44(95% CI 0.15 to 1.22)]
Anxiety Disorders – Panic Disorder	Andrisano et al. (2013)[15]	A systematic comparison of ADs rather than a meta-analysis 50 studies, 5236 patients	Mean change in panic symptoms from baseline	No statistical analysis; highlights inconsistencies and bias.
Anxiety Disorders – Social Anxiety Disorder	Mayo-Wilson et al. (2014)[16] High quality	Network meta-analysis Adheres to PRISMA guidelines 101 trials, N=13 164 (Including psychotherapy trials) Citalopram: 2 trials, N=54 Fluoxetine: 3 trials, N=107 Sertraline: 3 trials, N=535 Escitalopram: 2 trials, N=675 Venlafaxine: 5 trials, N=759	Calculated Standardised Mean Difference for each study vs waitlist and vs pill placebo (placebo controlled results in Appendix B of the article)	**Treatment effect (SMD) – reduction in social anxiety** Fluoxetine vs placebo -0,40 (95% CI -0,65 to -0,14) Escitalopram vs placebo -0,41 (95% CI -0,63 to -0,19) Sertraline vs placebo -0,45 (95% CI -0,65 to -0,25) Venlafaxine vs placebo -0,49 (95% CI -0,66 to -0,32) Citalopram vs placebo NS [-0,36(95% CI -0,77 to 0,05) Note: Citalopram RCTs study population not relevant to PICO question (i.e. cerebral blood flow on performing a public speaking task before and after intervention).
Schizophrenia – negative symptoms	Singh et al. (2010)[17]	Meta-analysis 23 trials, 819 participants	Change from baseline and end of trial mean scores of negative symptoms	Fluoxetine (NNT=11) and trazodone (NNT=6) may improve negative symptoms, but trial results are inconsistent. All studies are small.

Harmful effects				
Disorder / Patient population	**Author**	**Study design**	**Outcome measure**	**Results / Effect size**
Any harmful effects	Gartlehner et al. (2008)[18]	Systematic review and meta-analysis 83 RCTs with > 17 000 participants 21 observational studies with >740 000 participants	Suicide / self-harm	RCT sample sizes too small to detect differences between ADs One *retrospective* study cohort in UK: venlafaxine higher risk than citalopram (hazard ratio: 2.44; 95% CI 1.12 to 5.31) or fluoxetine (hazard ratio: 2.85; 95% CI 1.37 to 5.94).
			Sexual dysfunction	One large prospective observational study –citalopram & paroxetine & venlafaxine had highest incidence; mirtazapine and nefazodone the lowest (bupropion not included in study) One cross-sectional study – paroxetine highest; bupropion lowest.
			Seizures	Insufficient evidence to draw conclusions. Two open label trials showed no increased risk with bupropion than other ADs (N of participants not provided). One chart review of 538 self-poisoning with ADs – increased risk with venlafaxine.
			Fatal toxicity	UK database analysis – highest for venlafaxine (13.2 deaths / 1 million prescriptions)
			Other serious AEs	Case reports only – insufficient evidence to distinguish ADs
			General tolerability	Most AEs mild and similar across ADs British event monitoring study – fluvoxamine > other SSRIs
			Discontinuation due to AEs	Venlafaxine > SSRIs (RR 1.42; 95% CI 1.15 to 1.75)
			Weight gain	Paroxetine > fluoxetine (p=0.015) and >> sertraline (p<0.001)
			Cardiovascular AEs	Venlafaxine – significantly higher diastolic BP and HR vs fluoxetine & sertraline (p value or RR not provided)
Suicidality and aggression	Sharma et al (2016)[19]	Meta-analysis of clinical studies and trial reports 70 trials, N=18 526 Medicines included:	All-cause mortality	9 trials (N=2944) of medication vs placebo analysed – no significant increase in mortality in any trial and overall. [OR 1.28 (95% CI 0.40 to 4.06)] All deaths were in adults.

		Duloxetine 23 trials Fluoxetine 3 trials Paroxetine 8 trials Sertraline 28 trials Venlafaxine 8 trials The main article does not indicate which trial is of which antidepressant and supplementary data could not be accessed online. Risks re children and adolescents must be interpreted with caution. This phenomenon has been reported only in short term trials and its relevance is controversial.[20] Although SSRIs may increase suicidal ideation, lower rates of SSRI prescribing to children and adolescents have been associated with higher completed suicides in population level studies.[21] It is also possible that the depression may be due to undiagnosed bipolar disorder and the increased suicidality and aggression may be related to the negative antidepressant effect on bipolar depression.[20] Re individual antidepressants, Pompili et al[20] report paroxetine and venlafaxine as having a higher risk in their narrative review.	Suicides Suicidality – includes suicides, suicide attempts and suicide ideation Aggression Akathisia	5 suicides occurred out of all the trials, all in adults; 2 in placebo and 3 in medication groups, no significant difference [OR 0.58 (95% CI 0.07 to 4.48)] **Adults:** 31 trials analysed; no significant difference vs placebo in any trial or overall [OR 0.81 (95% CI 0.51 to 1.28). **Children and adolescents:** 11 trials analysed (2 of which had fraudulent data); only one ('Trial 27') had a significant increase vs placebo OR 4.76 (95% CI 1.25 to 18.14) However overall effect is increased: OR 2.39 (95% CI 1.31 to 4.33) Duloxetine and imipramine are mentioned in the narrative, but no connection is made with age group. **Adults:** 23 trials analysed; no significant difference vs placebo in any trial or overall [OR 1.09 (95% CI 0.55 to 2.14)] **Children and adolescents**: 9 trials analysed (excluding 2 with fraudulent data); only one ('Trial 27') had a significant increase vs placebo OR 7.41 (95% CI 1.64 to 33.47). However, overall effect is increased OR 2.19 (95% CI 1.17 to 4.11) Sertraline, paroxetine and fluoxetine are mentioned in the narrative, but no connection is made with age group. No significant difference vs placebo – all age groups.
Sexual dysfunction in MDD	Reichenpfauder et al. (2014)[22]	Network meta-analysis of 37 RCTs with 14 576 participants and analysis of 5 observational studies	Any reported sexual dysfunction	Vs Bupropion (medicine with lowest risk), escitalopram has highest risk of sexual dysfunction, followed by sertraline (OR > 1 favours the initial medication):

	High quality	Strength of evidence rated as low Comparisons indirect; wide confidence intervals High variability of reporting of sexual dysfunction High heterogeneity between studies But finding re bupropion consistent with other analyses and with being an NDRI		Bupropion vs escitalopram: OR 3.08 (95% CI 1.27 to 6.45) Bupropion vs sertraline: OR 2.21 (95% CI 1.07 to 4.12) Bupropion vs fluoxetine: NS [OR 1.02; 95% CI 9.42 to 2.11) However: Fluoxetine vs sertraline: NS [OR 2.44 (95% CI 0.94 to 5.26)] Escitalopram vs fluoxetine: NS [OR 0.37 (95% CI 0.13 to 0.85)] Escitalopram vs sertraline: NS [OR 0.79 (95% CI 0.39 to 1.54)]
Congenital malformations after use in pregnancy	Grigoriadis et al (2013)[23] High quality	Systematic Rev & meta-analysis of cohort and case control studies 27 studies included	Any congenital malformation (12 studies) Major congenital malformation Cardiovascular malformations (13 studies) Septal defects (9 studies)	Pooled studies: no increased risk 0.93 (95% CI, 0.85 to 1.02; p = 0.113) across ADs Pooled studies: no increased risk across ADs (RR = 1.07; 95% CI, 0.99 to 1.17; p = 0.095) Pooled risk small but significant (RR = 1.36; 95% CI, 1.08 to1.71; p = 0.008). Higher risk with Paroxetine(RR = 1.43; 95% CI, 1.08 to 1.88; p = 0.012) Pooled risk increased (RR = 1.40; 95% CI, 1.10–1.77; P = .005)

Antidepressants in PLWHA				
Depression in PLWHA	Lofgren et al. (2017)[24]	Systematic review of various intervention	Depression symptoms Relative reduction (pre-post): Net reduction compared with controls	Psychotherapy: 79%: 39% (3 studies) Task-shifting psychotherapy: 47%: 34% (4 studies) Antidepressants: 79%: 39% in controls (3 studies) Task-shifting ADs: Feasibility studies, no controls – overall reduced depression of 82% Exercise: 66%: 44% Other psychosocial interventions: 44%: 21% Studies highly variable; measures unclear But no serious AEs with ADs and task-shifting of ADs appears feasible.
Depression in PLWHA	Wagner et al. (1996)	Secondary analyses of data pooled from trials	Improvement after 2 and 6 weeks of treatment according to the Hamilton Depression Rating Scale (HDRS)	<u>Change in HDRS scores after 2 weeks of treatment (mean ± SD</u> • Imipramine: 11.8±3.8, p=0.002 • Fluoxetine:8.6±3.7, p=0.000

				• Sertraline:7.3±3.9, p=0.000 • Dextroamphetamine 6.4±4.1, p=0.001 • Placebo: 10.4±4.9, p=0.000 <u>Change in HDRS scores after 6 weeks of treatment (mean ± SD</u> • Imipramine: 5.7±4.6, p=0.000 • Fluoxetine:7.0±4.4, p=0.000 • Sertraline:5.2±4.5, p=0.000 • Dextroamphetamine 3.8±3.5, p=0.001 • Testosterone: 5.5±4.8, p=0.000 • Placebo: 9.9±6.8, p=0.000 Small trials; very heterogenous.
Pharmacotherapy in PLWHA	Hill & Lee (2013)[25]	Review of literature – antidepressants and antipsychotics	Reduction in depression symptoms 11 RCTs.	Fluoxetine most studied with significant efficacy (p<0.05) and no serious AEs. Four case reports of potential serotonin syndrome from fluoxetine + ritonavir at high doses 400 – 1200mg / day (from CYP2D6 inhibition). Small studies of citalopram & sertraline did not meet inclusion criteria. Theoretical drug interactions re CYP2D6 and other enzymes of doubtful clinical significance. TCAs: Imipramine also effective – anticholinergic side effects problematic. TCAs increased by ritonavir – caution advised. Others: Venlafaxine may be increased by ritonavir via CYP2D6 inhibition with potential CVS effects Bupropion reduced by ritonavir and efavirenz Conclusion: Adjust doses according to clinical response / AEs

7. Alternative agents

Tricyclic antidepressants – equivalent efficacy but increased adverse effects.

Psychotherapy – maybe an alternative in selected patients and may be adjunctive.

Summary of the evidence and comments

In depression, fluoxetine is the most studied SSRI; in adults, juvenile depression and PLWHA. It is less studied in anxiety disorders. Regarding tolerability and severe adverse effects, there is little in the evidence to suggest it being poorly tolerated. However, this does not exclude patient level poor response or adverse reactions and an available alternative is advisable. In addition, most of the evidence is derived from RCTs, in which external validity is limited by stringent inclusion and exclusion criteria. As the evidence may not always be clinically valid, a choice of antidepressants is recommended given the heterogeneity and commonality of the conditions to be treated.

Evidence suggests that sertraline is more effective than fluoxetine in the acute treatment of depression and in the elderly with depression. For acute treatment of depression, escitalopram is more effective than citalopram (the doses that were used in the included studies are shown in Appendix 2) and, in only 2 studies, more effective than fluoxetine. However, in the elderly, escitalopram and fluoxetine did not separate from placebo, whereas sertraline was more effective (RR 1.28 (95% CI 1.07-1.51)). In addition, although for all SSRIs the increased risk of dizziness was not statistically significant; the risk was lowest for sertraline and highest with escitalopram.

For anxiety disorders overall, in terms of pre-post effect size, escitalopram appears to be most effective, followed by sertraline and then fluoxetine. For GAD, fluoxetine appears to be most effective, but this is based on only one trial with 90 participants. For response, sertraline was more effective than placebo whereas escitalopram was not; for remission both were effective with escitalopram having the greater effect size vs placebo. However, only escitalopram had significantly more withdrawals than placebo because of adverse effects (OR 2.86 (95% CI 1.64 to 4.76)). None of the included trials assessed citalopram in GAD. In Social Anxiety Disorder, sertraline, escitalopram and fluoxetine were all more effective than placebo, with very little obvious difference between them although sertraline had the strongest effect size.

Regarding harmful effects, venlafaxine and paroxetine are most consistently associated with adverse effects. There is little to choose between fluoxetine, sertraline and escitalopram, apart from the higher risk of dizziness in the elderly and the significantly increased drop-outs due to side effects in GAD with escitalopram.

For palliative care and in people with comorbid medical illness there is little to guide the choice of SSRI. Fluoxetine has been most studied in PLWHA and appears generally safe, although serotonin syndrome has been documented with high doses of ritonavir. All the SSRIs inhibit certain P450 enzymes, and all may be affected by P450 enzyme inhibitors. Where the risk of serotonin syndrome is a concern, it is probably advisable to use an alternative to fluoxetine because of its 3-week half-life, and to use the lowest effective dose.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [x] Not confident [ ] Uncertain [ ]</td><td>For depression: Sertraline appears most effective in adults[6, 26] and in elderly[10]; fluoxetine maybe more effective in adolescents[12] and is more studied in HIV[25].

For anxiety: No evidence for citalopram.[13, 14, 16]

Fluoxetine possibly more effective and sertraline better tolerated[14].</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [x] No [ ]
List the members of the group.
Depression: sertraline, fluoxetine, excitalopram. Anxiety disorders: fluoxetine, sertraline, escitalopram,
List specific exclusion from the group:
Depression:
Anxiety: Citalopram</td><td>Rationale for therapeutic alternatives included:

References:

Rationale for exclusion from the group:

References:</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [x]

Is the option acceptable to key stakeholders?
Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [x]</td><td>Cost of medicines/ month:
<table><tr><td>Fluoxetine 20 mg, 30 caps</td><td>R 5.57*</td></tr><tr><td>Sertraline 50 mg, 30 tabs</td><td>R 46.34 to 92.69**</td></tr><tr><td>Escitalopram 10 mg, 30 tabs</td><td>R 27.99 to 55.98**</td></tr><tr><td>Citalopram 20 mg, 30 tabs</td><td>R 7.52*</td></tr></table>*Contract circular HP09-2016SD (accessed 1June2018)
** SEP Database, 5Jun2018 – 30 to 60% of average SEP</td></tr>
</table>

<table>
<tr><td></td><td></td><td>International price comparison
- International Medicines Price Guide, 2015[1] inflated using SEP adjustments for 2015-8[2]:
<table>
<tr><th>Medicine</th><th>Source (USA$ per unit)</th><th>ZAR[3] per unit</th><th>ZAR per month (30 days)</th></tr>
<tr><td>Fluoxetine 20mg</td><td>0.0083*</td><td>0.128</td><td>3.844</td></tr>
<tr><td>Sertraline 50 mg</td><td>0.0185*</td><td>0.286</td><td>8.57</td></tr>
<tr><td>Citalopram</td><td>n/a</td><td>n/a</td><td></td></tr>
<tr><td>Escitalopram</td><td>n/a</td><td>n/a</td><td></td></tr>
</table>
* PERU (DDP)

Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☒	☐

[1] Management Sciences for Health: International Medicines Price Guide, 2015. http://mshpriceguide.org/en/home/

[2] NDoH SEP adjustment notices (2015-2018)

[3] OANDA Average exchange rates: Period 1Jan2018 to 25Jun2018. https://www.oanda.com/currency/average

Recommendation

Based on this evidence review, the Primary Health Care Committee recommends that fluoxetine be used as first line for depression and anxiety in all patients. Sertraline, citalopram, and escitalopram are suitable alternatives if fluoxetine is poorly tolerated. The decision regarding which SSRI to use as second line for depression and anxiety should be based on cost.

Rationale: To simplify treatment of mental health conditions at primary health care, it would be preferable to have one first-line SSRI to treat both depression and anxiety. This SSRI should ideally work well across all populations, including children, adolescents, adults, the elderly, and those with co-morbidities, especially HIV. As SSRIs might be poorly tolerated, there should be an alternative SSRI for those who are unable to tolerate the first line SSRI.

Fluoxetine is relatively well-studied and is effective for depression in adults, adolescents, and HIV-infected patients. It is effective for GAD, and for anxiety in HIV-infected patients. It is also reasonably well-tolerated.

In terms of a second line SSRI, escitalopram, citalopram, and sertraline are all effective in depression. Sertraline is the most effective for depression in elderly patients. Sertraline and escitalopram are also effective in anxiety. The included studies did not assess citalopram in GAD, but there is evidence of its benefit in Panic Disorder. Assuming that citalopram is comparable to escitalopram in equivalent doses, citalopram, escitalopram, or sertraline may be used as second line treatment in anxiety, as for depression.

Level of Evidence: I Systematic reviews and meta-analyses

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
	X	X

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations

Research priorities

References:

1. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):1357-66. 10.1016/S0140-6736(17)32802-7
2. Magni LR, Purgato M, Gastaldon C, Papola D, Furukawa TA, Cipriani A, et al. Fluoxetine versus other types of pharmacotherapy for depression. The Cochrane database of systematic reviews. 2013(7):CD004185. 10.1002/14651858.CD004185.pub3
3. Cipriani A, Purgato M, Furukawa TA, Trespidi C, Imperadore G, Signoretti A, et al. Citalopram versus other anti-depressive agents for depression. The Cochrane database of systematic reviews. 2012(7):CD006534. 10.1002/14651858.CD006534.pub2
4. Cipriani A, Santilli C, Furukawa TA, Signoretti A, Nakagawa A, McGuire H, et al. Escitalopram versus other antidepressive agents for depression. The Cochrane database of systematic reviews. 2009(2):CD006532. 10.1002/14651858.CD006532.pub2
5. Cipriani A, La Ferla T, Furukawa TA, Signoretti A, Nakagawa A, Churchill R, et al. Sertraline versus other antidepressive agents for depression. The Cochrane database of systematic reviews. 2010(1):CD006117. http://dx.doi.org/10.1002/14651858.CD006117
6. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373(9665):746-58. 10.1016/S0140-6736(09)60046-5
7. Wang Y, Yu L, Xie J, Chen J, Wei Q. Comparative efficacies of fluoxetine and paroxetine in major depression across varying acute-phase treatment periods: a meta-analysis. Asia Pac Psychiatry. 2014;6(4):353-62. 10.1111/appy.12106
8. Katzman MA, Tricco AC, McIntosh D, Filteau MJ, Bleau P, Chokka PR, et al. Paroxetine versus placebo and other agents for depressive disorders: a systematic review and meta-analysis. The Journal of clinical psychiatry. 2007;68(12):1845-59 https://www.ncbi.nlm.nih.gov/pubmed/18162015
9. Hansen R, Gaynes B, Thieda P, Gartlehner G, Deveaugh-Geiss A, Krebs E, et al. Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. Psychiatric services. 2008;59(10):1121-30. 10.1176/appi.ps.59.10.1121 10.1176/ps.2008.59.10.1121

10. Thorlund K, Druyts E, Wu P, Balijepalli C, Keohane D, Mills E. Comparative efficacy and safety of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in older adults: a network meta-analysis. Journal of the American Geriatrics Society. 2015;63(5):1002-9. 10.1111/jgs.13395
11. Seitz DP, Gill SS, Conn DK. Citalopram versus other antidepressants for late-life depression: a systematic review and meta-analysis. International journal of geriatric psychiatry. 2010;25(12):1296-305. 10.1002/gps.2483
12. Tsapakis EM, Soldani F, Tondo L, Baldessarini RJ. Efficacy of antidepressants in juvenile depression: meta-analysis. The British journal of psychiatry : the journal of mental science. 2008;193(1):10-7. 10.1192/bjp.bp.106.031088
13. Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. International clinical psychopharmacology. 2015;30(4):183-92. 10.1097/YIC.0000000000000078
14. Baldwin D, Woods R, Lawson R, Taylor D. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. Bmj. 2011;342:d1199. 10.1136/bmj.d1199
15. Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: a meta-analysis. International clinical psychopharmacology. 2013;28(1):33-45. 10.1097/YIC.0b013e32835a5d2e
16. Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):368-76. 10.1016/S2215-0366(14)70329-3
17. Singh SP, Singh V, Kar N, Chan K. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. The British journal of psychiatry : the journal of mental science. 2010;197(3):174-9. 10.1192/bjp.bp.109.067710
18. Gartlehner G, Thieda P, Hansen RA, Gaynes BN, Deveaugh-Geiss A, Krebs EE, et al. Comparative risk for harms of second-generation antidepressants : a systematic review and meta-analysis. Drug Saf. 2008;31(10):851-65 https://www.ncbi.nlm.nih.gov/pubmed/18759509
19. Sharma T, Guski LS, Freund N, Gotzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. Bmj. 2016;352:i65. 10.1136/bmj.i65
20. Pompili M, Serafini G, Innamorati M, Ambrosi E, Giordano G, Girardi P, et al. Antidepressants and Suicide Risk: A Comprehensive Overview. Pharmaceuticals (Basel). 2010;3(9):2861-83. 10.3390/ph3092861
21. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. The American journal of psychiatry. 2006;163(11):1898-904. 10.1176/ajp.2006.163.11.1898
22. Reichenpfader U, Gartlehner G, Morgan LC, Greenblatt A, Nussbaumer B, Hansen RA, 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(1):19-31. 10.1007/s40264-013-0129-4
23. Grigoriadis S, VonderPorten EH, Mamisashvili L, Roerecke M, Rehm J, Dennis CL, et al. Antidepressant exposure during pregnancy and congenital malformations: is there an association? A systematic review and meta-analysis of the best evidence. The Journal of clinical psychiatry. 2013;74(4):e293-308. 10.4088/JCP.12r07966
24. Lofgren SM, Nakasujja N, Boulware DR. Systematic Review of Interventions for Depression for People Living with HIV in Africa. AIDS Behav. 2017. 10.1007/s10461-017-1906-3
25. Hill L, Lee KC. Pharmacotherapy considerations in patients with HIV and psychiatric disorders: focus on antidepressants and antipsychotics. Ann Pharmacother. 2013;47(1):75-89. 10.1345/aph.1R343
26. Cipriani A, Furukawa TA, Geddes JR, Malvini L, Signoretti A, McGuire H, et al. Does randomized evidence support sertraline as first-line antidepressant for adults with acute major depression? A systematic review and meta-analysis. The Journal of clinical psychiatry. 2008;69(11):1732-42 https://www.ncbi.nlm.nih.gov/pubmed/19026250

APPENDIX I: Articles not included on abstract screening in SSRI review for PHC and Adult Hospital Level STGs

	No comparison between SSRIs
1	Knapp P, Campbell Burton CA, Holmes J, Murray J, Gillespie D, Lightbody CE, et al. Interventions for treating anxiety after stroke. Cochrane Database Syst Rev. 2017;5:CD008860.
2	Jakobsen JC, Katakam KK, Schou A, Hellmuth SG, Stallknecht SE, Leth-Moller K, et al. Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. BMC Psychiatry. 2017;17(1):58.
3	Curtiss J, Andrews L, Davis M, Smits J, Hofmann SG. A meta-analysis of pharmacotherapy for social anxiety disorder: an examination of efficacy, moderators, and mediators. Expert Opin Pharmacother. 2017;18(3):243-51.
4	Allain N, Leven C, Falissard B, Allain JS, Batail JM, Polard E, et al. Manic switches induced by antidepressants: an umbrella review comparing randomized controlled trials and observational studies. Acta Psychiatr Scand. 2017;135(2):106-16.
5	Leichsenring F, Steinert C, Hoyer J. Psychotherapy Versus Pharmacotherapy of Depression: What's the Evidence? Z Psychosom Med Psychother. 2016;62(2):190-5.
6	Palmer SC, Natale P, Ruospo M, Saglimbene VM, Rabindranath KS, Craig JC, et al. Antidepressants for treating depression in adults with end-stage kidney disease treated with dialysis. Cochrane Database Syst Rev. 2016(5):CD004541.
7	Koslowski N, Klein K, Arnold K, Kosters M, Schutzwohl M, Salize HJ, et al. Effectiveness of interventions for adults with mild to moderate intellectual disabilities and mental health problems: systematic review and meta-analysis. Br J Psychiatry. 2016;209(6):469-74.
8	Fiest KM, Walker JR, Bernstein CN, Graff LA, Zarychanski R, Abou-Setta AM, et al. Systematic review and meta-analysis of interventions for depression and anxiety in persons with multiple sclerosis. Mult Scler Relat Disord. 2016;5:12-26.
9	Ostuzzi G, Matcham F, Dauchy S, Barbui C, Hotopf M. Antidepressants for the treatment of depression in people with cancer. Cochrane Database Syst Rev. 2015(6):CD011006.
10	Maguire MJ, Weston J, Singh J, Marson AG. Antidepressants for people with epilepsy and depression. Cochrane Database Syst Rev. 2014(12):CD010682.
11	Lorenzo L, Einarson A. Antidepressant use in pregnancy: an evaluation of adverse outcomes excluding malformation. Isr J Psychiatry Relat Sci. 2014;51(2):94-104.
12	Vernon JA, Grudnikoff E, Seidman AJ, Frazier TW, Vemulapalli MS, Pareek P, et al. Antidepressants for cognitive impairment in schizophrenia--a systematic review and meta-analysis. Schizophr Res. 2014;159(2-3):385-94
13	Zhou X, Qin B, Del Giovane C, Pan J, Gentile S, Liu Y, et al. Efficacy and tolerability of antidepressants in the treatment of adolescents and young adults with depression and substance use disorders: a systematic review and meta-analysis. Addiction. 2015;110(1):38-48.
14	Amos T, Stein DJ, Ipser JC. Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2014(7):CD006239.
15	Qin B, Zhang Y, Zhou X, Cheng P, Liu Y, Chen J, et al. Selective serotonin reuptake inhibitors versus tricyclic antidepressants in young patients: a meta-analysis of efficacy and acceptability. Clin Ther. 2014;36(7):1087-95 e4.
16	Borges S, Chen YF, Laughren TP, Temple R, Patel HD, David PA, et al. Review of maintenance trials for major depressive disorder: a 25-year perspective from the US Food and Drug Administration. J Clin Psychiatry. 2014;75(3):205-14.
17	Grigoriadis S, VonderPorten EH, Mamisashvili L, Eady A, Tomlinson G, Dennis CL, et al. The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. J Clin Psychiatry. 2013;74(4):e309-20.
18	Calati R, Salvina Signorelli M, Balestri M, Marsano A, De Ronchi D, Aguglia E, et al. Antidepressants in elderly: metaregression of double-blind, randomized clinical trials. J Affect Disord. 2013;147(1-3):1-8.
19	Wu Q, Qu W, Crowell MD, Hentz JG, Frey KA. Tricyclic antidepressant use and risk of fractures: a meta-analysis of cohort and case-control studies. J Bone Miner Res. 2013;28(4):753-63.
20	Mead GE, Hsieh CF, Lee R, Kutlubaev MA, Claxton A, Hankey GJ, et al. Selective serotonin reuptake inhibitors (SSRIs) for stroke recovery. Cochrane Database Syst Rev. 2012;11:CD009286.
21	Wilkinson P, Izmeth Z. Continuation and maintenance treatments for depression in older people. Cochrane Database Syst Rev. 2012;11:CD006727.
22	von Wolff A, Holzel LP, Westphal A, Harter M, Kriston L. Selective serotonin reuptake inhibitors and tricyclic antidepressants in the acute treatment of chronic depression and dysthymia: a systematic review and meta-analysis. J Affect Disord. 2013;144(1-2):7-15.
23	Hart SL, Hoyt MA, Diefenbach M, Anderson DR, Kilbourn KM, Craft LL, et al. Meta-analysis of efficacy of interventions for elevated depressive symptoms in adults diagnosed with cancer. J Natl Cancer Inst. 2012;104(13):990-1004.
24	Salter KL, Foley NC, Zhu L, Jutai JW, Teasell RW. Prevention of poststroke depression: does prophylactic pharmacotherapy work? J Stroke Cerebrovasc Dis. 2013;22(8):1243-51.
25	Kok RM, Nolen WA, Heeren TJ. Efficacy of treatment in older depressed patients: a systematic review and meta-analysis of double-blind randomized controlled trials with antidepressants. J Affect Disord. 2012;141(2-3):103-15.

26	Hauser W, Wolfe F, Tolle T, Uceyler N, Sommer C. The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. CNS Drugs. 2012;26(4):297-307.
27	Gibbons RD, Hur K, Brown CH, Davis JM, Mann JJ. Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. Arch Gen Psychiatry. 2012;69(6):572-9.
28	Tedeschini E, Levkovitz Y, Iovieno N, Ameral VE, Nelson JC, Papakostas GI. Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. J Clin Psychiatry. 2011;72(12):1660-8.
29	Richards BL, Whittle SL, Buchbinder R. Antidepressants for pain management in rheumatoid arthritis. Cochrane Database Syst Rev. 2011(11):CD008920.
30	Goncalves DC, Byrne GJ. Interventions for generalized anxiety disorder in older adults: systematic review and meta-analysis. J Anxiety Disord. 2012;26(1):1-11.
31	Wu Q, Bencaz AF, Hentz JG, Crowell MD. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. Osteoporos Int. 2012;23(1):365-75.
32	Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. Cochrane Database Syst Rev. 2011(9):CD008012.
33	Price A, Rayner L, Okon-Rocha E, Evans A, Valsraj K, Higginson IJ, et al. Antidepressants for the treatment of depression in neurological disorders: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry. 2011;82(8):914-23.
34	Kok RM, Heeren TJ, Nolen WA. Continuing treatment of depression in the elderly: a systematic review and meta-analysis of double-blinded randomized controlled trials with antidepressants. Am J Geriatr Psychiatry. 2011;19(3):249-55
35	Taylor D, Meader N, Bird V, Pilling S, Creed F, Goldberg D, et al. Pharmacological interventions for people with depression and chronic physical health problems: systematic review and meta-analyses of safety and efficacy. Br J Psychiatry. 2011;198(3):179-88.
36	Barbui C, Cipriani A, Patel V, Ayuso-Mateos JL, van Ommeren M. Efficacy of antidepressants and benzodiazepines in minor depression: systematic review and meta-analysis. Br J Psychiatry. 2011;198(1):11-6, sup 1.
37	Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M. Antidepressants for depression in physically ill people. Cochrane Database Syst Rev. 2010(3):CD007503.
38	Tondo L, Vazquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr Scand. 2010;121(6):404-14.
39	Donovan MR, Glue P, Kolluri S, Emir B. Comparative efficacy of antidepressants in preventing relapse in anxiety disorders - a meta-analysis. J Affect Disord. 2010;123(1-3):9-16.
40	Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, et al. Antidepressants versus placebo for depression in primary care. Cochrane Database Syst Rev. 2009(3):CD007954.
41	Gartlehner G, Gaynes BN, Hansen RA, Thieda P, DeVeaugh-Geiss A, Krebs EE, et al. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. Ann Intern Med. 2008;149(10):734-50.
42	Nelson JC, Delucchi K, Schneider LS. Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. Am J Geriatr Psychiatry. 2008;16(7):558-67
43	Papakostas GI, Montgomery SA, Thase ME, Katz JR, Krishen A, Tucker VL. Comparing the rapidity of response during treatment of major depressive disorder with bupropion and the SSRIs: a pooled survival analysis of 7 double-blind, randomized clinical trials. J Clin Psychiatry. 2007;68(12):1907-12.
44	Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. J Psychopharmacol. 2007;21(8):864-72.
	No pharmacological trials included
45	van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJ, Kamperman AM. Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis. PLoS One. 2017;12(3):e0173397.
	Protocol only
46	Sun X, Deng L, Qiu S, Tu X, Wang D, Liu M. Pharmacological and psychotherapeutic interventions for management of poststroke depression: A Bayesian network meta-analysis of randomized controlled trials. Medicine (Baltimore). 2017;96(7):e6100.

Studies rejected from HIV search

	Narrative review
1.	Watkins CC, Pieper AA, Treisman GJ. Safety considerations in drug treatment of depression in HIV-positive patients: an updated review. Drug Saf. 2011;34(8):623-39.
	Study withdrawn
1.	Gill D, Hatcher S. Antidepressants for depression in medical illness. Cochrane Database Syst Rev. 2000(4):CD001312.

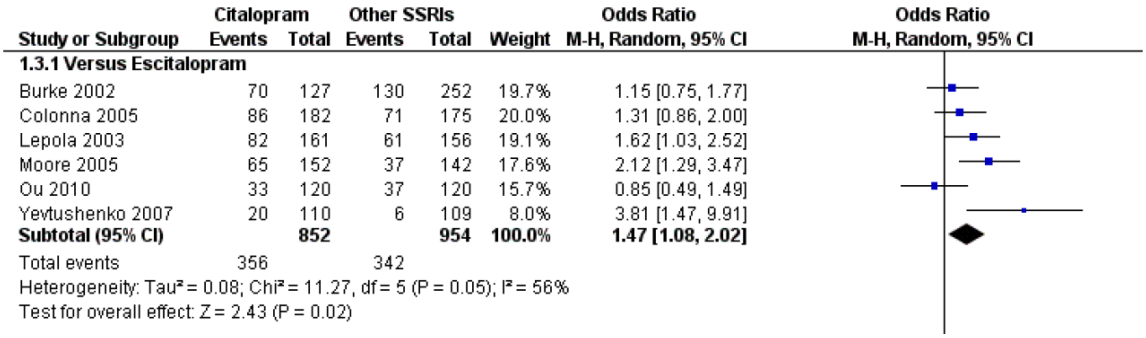
Appendix II: Doses of citalopram and escitalopram for depression and anxiety in head-to-head studies

A: DEPRESSION

- **Comparative efficacy**

Forest plot from Cipriani et al 2012[4]:

Figure 4. Forest plot of comparison: 1 Failure to respond at endpoint (6-12 weeks), outcome: 1.3 Citalopram versus other SSRIs.



- **Comparative doses**

Study	Citalopram daily dose	Escitalopram daily dose	Sponsor
Burke 2002	40 mg	10–20 mg	Escitalopram manufacturer
Colonna 2005	20 mg	10 mg	Escitalopram manufacturer
Lepola 2003	20–40 mg	10–20 mg	Escitalopram manufacturer
Moore 2005	40 mg	20 mg	Escitalopram manufacturer
Ou 2010	20 mg	10 mg	National Institutes of Pharmaceutical Research and Development
Yevtushenko 2007	10 and 20 mg	10 mg	OOO ARBACOM, relationship to manufacturer unclear

- **Recommended doses as per SAMF[5]:**

Citalopram 20-40 mg daily	Escitalopram 10-20 mg daily

B: ANXIETY

- **Comparative efficacy**

Only one trial assessed escitalopram and citalopram simultaneously, in patients with panic disorder[6 7]. The authors did not directly compare the treatments however, but compared each with placebo. The primary outcome was panic attack frequency at week 10. The log transformed mean difference from baseline at 10 weeks was -1.32±0.1 for placebo, -1.61±0.1 for escitalopram (p=0.04 versus placebo), and -1.43±0.1 for citalopram (not significant versus placebo, p value not reported). Both were significantly better than placebo in terms of improvements in symptoms.

- **Comparative doses**

Study	Citalopram daily dose	Escitalopram daily dose	Sponsor
Stahl 2003	First week 10 mg, then 20–40 mg (mean 21.3 mg)	First week 5 mg, then 10–20 mg (mean 10.8 mg)	Escitalopram manufacturer

- **Recommended doses as per SAMF[8]:**

Citalopram: 10 mg for 1 week, then 20-40 mg daily	Escitalopram: 5 mg for 1 week, then 10-20 mg daily

[4] Cipriani A, Purgato M, Furukawa TA, Trespidi C, Imperadore G, Signoretti A, et al. Citalopram versus other anti-depressive agents for depression. The Cochrane database of systematic reviews. 2012(7):CD006534.
[5] SAMF, 2016.
[6] Stahl SM, Gergel I, Li D. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2003 Nov;64(11):1322-7.
[7] Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol. 2015;30(4):183-92.
[8] SAMF, 2016.