Table 1B: Overview of Antidepressant Therapy for Post-Stroke Depression

This table provides a summary of the pharmacotherapeutic properties, side effects, drug interactions and other important information on select medications identified through the evidence reviews as the most frequently used medications for the management of post-stroke depression. This table should be used as a reference guide by health care professionals when selecting an appropriate agent for individual patients. Patient compliance, side effects, drug interactions and comorbidities should all be taken into consideration during decision-making, in addition to other information provided in this table and available elsewhere regarding these medications.

	Selective Serotonin Reuptake Inhibitors (SSRI)	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Other
Medication Generic and Trade Names	citalopram – Celexa escitalopram – Cipralex fluoxetine – Prozac fluvoxamine - Luvox paroxetine – Paxil sertraline - Zoloft	duloxetine - Cymbalta milnacipran – not available in Canada reboxetine – special access program only venlafaxine – Effexor	methylphenidate – Ritalin (amphetamine) nortriptyline – Aventyl (tricyclic antidepressant) trazodone – Desyrel, PMS-, Apo-, Dom-, Mylan-, Nu-, Phl-, ratio-, Teva-trazodone (tetracylic antidepressant)
Contra-indications	Fluoxetine – intracranial hemorrhage All- Hypersensitivity to SSRIs, or taking Monoamine oxidase inhibitors (MAOIs)	Hypersensitivity, patients with a seizure disorder, or taking MAOIs	Nortriptyline – cardiac abnormalities Hypersensitivity, patients with uncontrolled narrow angle glaucoma, or patients taking: MAOIs, certain antibiotics , CYP1A2 inhibitors (eg. fluvoxamine and quinolones)
Side Effects	SSRI: Serotonin syndrome, sedation, increased risk for seizures (0.2% incidence), bleeding, and hyponatremia fluoxetine: interacts with certain cardiac medication e.g. clopidogrel most severely, nimodipline, and beta-blockers Generally reported: dry mouth, loss of appetite and weight-loss, nausea, dizziness, loss of libido, constipation or diarrhea, insomnia or somnolence,	Venlafaxine - Increases in heart rate can occur by 3-4bpm, QTc arrhythmia at 75-225mg/day. Duloxetine - been associated with an increase in blood pressure and clinically significant hypertension in some patients Generally reported: dry mouth, loss of appetite and weight-loss, loss of libido, constipation, nausea, insomnia, dizziness anxiety, sweating	nortriptyline – may increase risk of delirium in stroke patients; serotonin syndrome, ventricular arrhythmias and orthostatic hypotension Generally reported: dry mouth, loss of appetite and weight-loss, loss of libido, constipation, nausea, dizziness, anxiety, somnolence, sweating

	Selective Serotonin Reuptake Inhibitors (SSRI)	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Other
	sweating		
Landmark Trials	citalopram[6,14], fluvoxamine[8], fluoxetine[1-5,14] sertraline[7,14] paroxetine[9]	reboxetine[10], milnacipran[11], venlafaxine[12], duloxetine[14]	trazodone[15,16], nortriptyline[17,18] methylphenidate[19]
Inclusion / Exclusion Criteria & Depression severity	First ever and recurrent strokes Mild depression[5, 7, 8] Moderate depression[1,2,4,5,6] Severe depression[3, 9, 14]	SNRI: PSD following from first ever stroke. Reboxetine: only severe "retarded depression" in first ever stroke. Milnacipran: mild depression, prior depression or antidepressant use was excluded. Venlafaxine: moderate depression Duloxetine: severe depression	First ever and recurrent strokes trazodone: mild[15] and moderate[16] depression nortriptyline: mild[17] and moderate[18] depression methylphenidate: moderate depression
Dose ranges tested	fluoxetine: 10 - 40mg /day (including variable dose study)citalopram: 20 – 60mg/ day escitalopram: 10 – 20mg/day sertraline: 50 - 100mg/day	venlafaxine: 75 – 150 mg/day reboxetine: 4mg/ 2x day milnacipran: 50 – 100mg/day duloxetine: 60 – 120mg/day	trazodone: 200 – 300mg/day mirtazepine: 30mg/day nortriptyline: 20 – 100mg/day
Summary of Findings	mild: 1 negative, 1 positive studies moderate: 2 negative, 3 positive studies severe: 1 negative, 3 positive studies Level 1 RCT evidence supports the efficacy of SSRIs fluoxetine and citalopram for treatment of moderate to severe post-stroke depression.	mild: 2 positive studies moderate: 1 positive studies severe: 1 positive studies Studies were open-label or uncontrolled; no level 1 RCT evidence available to support efficacy of SNRI for treatment of post-stroke depression.	mild: 2 positive studies moderate: 3 positive studies severe: no studies Level 1 RCT evidence available to support nortriptyline and methylphenidate for treatment of post-stroke depression.
Other Outcomes	Prevention of PSD: fluoxetine, escitalopram and sertraline studied	Anxiety in PSD: duloxetine more effective than citalopram in treating	Mortality & PSD: increased survival of depressed and non-depressed

	Selective Serotonin Reuptake Inhibitors (SSRI)	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Other
	as prophylaxis Mortality & PSD: increased survival of depressed and non-depressed treated with fluoxetine or nortriptyline over placebo in 9-year follow-up[1] Executive function: maintenance of executive function compared to placebo over 21 months follow-up[2]; no improvement of executive function Sleep: fluvoxamine improved sleep disturbances as measured by peripheral melatonin blood levels.	anxiety symptoms Alexithymia: venlafaxine results in greater improvement of emotional awareness than fluoxetine	treated with fluoxetine or nortriptyline over placebo in 9-year follow-up[3] Functional status (ADLs): trazodone treatment resulted in trending improvement
Safety	Discontinuation: Discontinuation of escitalopram may increase poststroke depressive symptoms over 6 months[4] Cerebrovascular AE: rare (<1/1000) in fluoxetine, infrequent to rare (1/100 to 1/1000) for other SSRIs but vigilance required for use in high-risk bleeding & vasoconstrictive stroke.[5] Geriatric: anticholinergic effects and orthostatic hypotension can be particularly problematic in older patients, resulting in increased risk of	Duloxetine: should be used with caution in patients with uncontrolled hypertension as it may expose them to hypertensive crisis	Trazodone: serious warning for priapism, associated with increased risk of syncope and falls, particularly in older patients Nortriptyline: special consideration for geriatric population with orthostatic hypotension and anticholinergic effects; caution is advised if used in patients with a personal or family history of cardiovascular disease, arrhythmias or conduction disturbances

[i] Jorge, *Am J Psychiatry* 2003 Oct;160(10):1823-9
[2] Narushima, *B J Psych* 2007, 190:260-265
[3] Jorge, *Am J Psychiatry* 2003 Oct;160(10):1823-9
[4] Mikami, *Stroke* 2011*; Aug 42:3281-3283*
[5] Ramasubbu, *J Clin Psychiatry* 2004; 64:1642-1653

	Selective Serotonin Reuptake Inhibitors (SSRI)	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Other
	cognitive impairment, confusion, urinary retention and falls. Delirium : anticholinergic effects may play role in delirium in acute stroke patients[6]		
$ per month/ coverage in Canada	citalopram $0.33/day (regular benefit) escitalopram $1.84 (regular benefit) fluoxetine (20mg) $0.46 (regular benefit) paroxetine – (20mg) $0.45 and (30mg) $0.4796 sertraline - (25mg) $0.20 and ~(100mg) $0.40 fluvoxamine - (50mg) $0.21 and (100mg) $0.38	duloxetine – Cymbalta (30mg) $1.89 and (60mg) $3.79 milnacipran – not available reboxetine - not readily available, not covered by provincial drug coverage plans venlafaxine $0.3469/day (regular benefit)	methylphenidate – $0.28-$4.18 (10-80mg) trazodone ~$0.10/day (regular benefit)

[6] Caeiro, *Eur J. of Neurology* 2004; 11: 699–704

Appendix One: Pharmacotherapy Trials

Ref No.	Class	Drug	Reference	Patients (Treated/ Control)	Depression Severity (Treated/Control)	Treatment (wks)	Dose (mg/day)	Drop-out	+/-	Finding	AEs of treated group
1	SSRI	Fluoxetine (randomized, uncontrolled)	Cravello (2009) ‡	25	moderate; baseline HAM-D: 19;	8	20-40		+	improvement in depressive symptoms similar to venlafaxine	
2	SSRI	Fluoxetine	Choi-Kwon (2006)	76/76	moderate; baseline BDI: 19	12	20	15/76	-	not significant on PSD, but improvements observed in emotional disturbances	10 AE, 1 hospitalizatio n
3	SSRI	Fluoxetine	Freuhwald (2003)	28/ 26	severe; baseline HAM-D: 33/30	12	20-40	4/50	-	non-significant over placebo in 3 months, significant lowered depression at 18 months open-label follow-up	none detected
4	SSRI	Fluoxetine	Robinson (2000)	23 / 17	moderate; baseline HAM-D: 20/18	12	10-40	13/23	-	no significant differences between fluoxetine and placebo in depression	Weight loss, Anxiety, Insomnia GI symptoms
5	SSRI	Fluoxetine	Wiart (2000)	16/15	moderate; MDD by ICD-10 and MADRS ≥ 19; baseline MADRS: 29/27	6.5	20	2/31	+	significant improvement in depression	1 AE of transient increase of transaminase s; well-tolerated
6	SSRI	Citalopram	Anderson (1994)	33/33	moderate; baseline HAM-D: 19/19	6	10 – 20 up to 60		+	significant reduction of depression, fewer meet HAM-D depression criteria at endpoint	1 death, 6 AE, 3 strokes
7	SSRI	Sertraline	Murray (2002)	62/61	mild; mean baseline MADRS: 19/20	26	50 – 100	54/123	-	no significant improvement on depression; sertraline	8 AE

Ref No.	Class	Drug	Reference	Patients (Treated/ Control)	Depression Severity (Treated/Control)	Treatment (wks)	Dose (mg/day)	Drop-out	+/-	Finding	AEs of treated group
										found superior only in emotional distress, and QoL	
8	SSRI	Fluvoxamine	Sunami (2012) †	19 / 10	mild; ZDS ≥ 40; baseline ZDS: 47/47	4	25-75	3/9 T	+	improved sleep disturbance & depressive scores; no change in cognition	not reported
9	SSRI	Paroxetine (uncontrolled)	Horvath (2006) †‡	788	severe; baseline HAM-D: 25	8	20-40	10%	+	mean HAM-D decreased from 25 to 12 by 3rd week, 9 by 8th week of treatment. Depressive scores decreased further by follow-up at 26 weeks.	8.2% AE: nausea/vomiting, dizziness, headaches and diarrhea 1.9% of SAE
10	SNRI	Reboxetine	Rampello (2005)†	16/15	severe; baseline HAMD: 24/24; baseline BDI: 21/20	16	8	0	+	significant improvement of retarded depressed patients	dryness of faeces, constipation, hyper perspiration
11	SNRI	Milnacipran (open label, unblended, historical control)	Yamakawa (2005)†‡	11	mild; DSM-IV MDD or MinD; baseline ZDS: 52/53;	varied on length of stay	30-60	0	+	significant improvement in self-reported depression compared to the historical control group; no change in ADLS.	no AE's reported
12	SNRI	Venlafaxine (randomized, uncontrolled)	Cravello (2009) ‡	25	moderate; baseline HAM-D: 17;	8	75-150	0?	+	improvement in depressive symptoms on venlafaxine similar to fluoxetine, venlafaxine results in greater improvement on alexithymia severity	
14	SNRI	Duloxetine, Citalopram,	Karaiskos (2012)†‡	D20 /C20 /S20	severe; DSM-IV mood disorder,	12	60-120/ 20-40/		+	duloxetine more effective than	not significantly

Ref No.	Class	Drug	Reference	Patients (Treated/ Control)	Depression Severity (Treated/Control)	Treatment (wks)	Dose (mg/day)	Drop-out	+/-	Finding	AEs of treated group
		Sertraline			depressive episode; baseline HAM-D: 25/24/24		50-200			citalopram and sertraline for anxiety symptoms in PSD; all 3 AD were effective at treating depressive symptoms	different from citalopram or sertraline. 15% for somnolence and nausea
15	Other	Trazodone	Raffaele (1996)	11/11	mild; baseline ZDS: 59/62;	5	300		+	trazodone significantly improved self-reported depression; not significant in placebo.	6 AE
16	Other	Trazodone	Reding (1986)	27	moderate; DSM-3 MDD or dysthymic disorder or "abnormal" ZDS baseline: 62/66	4-5	200		+	trazodone trends towards better functional status (ADLS) for depressed patients (depressive severity was NOT primary outcome)	
17	Other	Nortriptyline	Robinson (2000)	14/17	moderate; baseline HAM-D: 23/18	12	25- 100	5/14	+	nortriptyline higher response rate than fluoxetine or placebo	sedation, rash
18	Other	Nortriptyline	Lipsey (1984)	14/20	mild; baseline HAM-D: 14/17;	4	20 – 100	8/34	+	improvement of MDD, reduction of depression with nortriptyline over placebo	
19	Other	Methylpheni-date	Grade (1998)	10/11	moderate; baseline HAM-D: 20/25;	3	5-60		+	significant lower depressive scores compared to placebo	

† The outcome assessor was not blinded
‡Open-label study

ADL = Activities of Daily Living; AE = adverse event; BDI = Beck Depression Inventory; DSM = Diagnostic and Statistical Manual of Mental Disorders; HAM-D = Hamilton Depression Rating Scale; ICD-10 = International Classification of Diseases, 10th Revision; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = Major Depressive Disorder; MinD = Minor Depressive Disorder; QoL = Quality of Life; SNRI = Selective Noradrenaline Reuptake Inhibitor; SSRI = Selective Serotonin Reuptake Inhibitor; ZDS = Zung Depression Scale

Appendix Two: PSD Prophylaxis Trials of Non-depressed patients

Ref No.	Class	Drug	Reference	Patients (Treated/Control)	Treatment weeks	Dosing schedule (mg/day)	Drop-out	+/-	Finding	AEs of treated group
5	SSRI	Fluoxetine	Chollet (FLAME) (2011)	57/56	12	20		+	significant lower frequency of depression at endpoint than placebo	hypoatronemia, transient digestive disorders, partial seizure
3	SSRI, Other	Fluoxetine, Nortriptyline	Narushima (2002)	17/15/16	12	F: 10 – 40 N: 25-100	2	-	no significant treatment effect on intention to treat; significant effect observed in completed patients	
6	SSRI, TCA	Nortriptyline Fluoxetine	Robinson (2000)	13/13/15	12	N: 25-100 F: 10-40		-	no significant treatment effect	
2	SSRI	Sertraline	Almeida (2006)	55/56	24	50	29/56	-	no improvement of depression over placebo	
1	SSRI	Sertraline	Rasmussen (2003)	70/67	52	50-150	49%	+	significantly fewer treated developed MDD (HAM-D > 18) compared to placebo ; superiority starts at 6 - 21 weeks	treated had significantly fewer AE
4	SSRI	Escitalopram (unblinded)	Robinson (2008)	59/58	52	10	15/149	+	significantly fewer on escitalopram or problem-solving therapy developed MDD or minor episodes compared to placebo	decreased libido, fatigue, GI symptoms
7	SNRI	Milnacipran	Tsai (2001)[7]	46/46	52	50 - 100	21/46	+	significant for preventing PSD in the first year following a stroke	no significant difference from placebo
8	SNRI	Duloxetine (single-blinded)	Zhang (2013)†[8]	47/48	12	30-90	12/48	+	significantly lower incidence of mind and MDD with duloxetine. Significant higher ADL and QoL scores than placebo at endpoint	nausea, vomiting

[7] Int Clin Psychopharmacol. 2011 Sep;26(5):263-7
[8] Eur Neurol. 2013;69(6):336-43. doi: 10.1159/000345374.

9	Other	Mirtazepine (open-label)	Niedermaier (2005)‡	66/64	52	52	30	+	significantly fewer developed PSD when treated mirtazepine (2) over no treatment (14)

† The outcome assessor was not blinded
‡Open-label study