CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

MOOD, COGNITION AND FATIGUE FOLLOWING STROKE

Table 1C: Summary Table for Selected Pharmacotherapy for Post-Stroke Depression

Update 2019

Lanctôt KL, Swartz RH (Writing Group Chairs) on Behalf of the Canadian Stroke Best Practice Recommendations Mood, Cognition and Fatigue following Stroke Writing Group and the Canadian Stroke Best Practice and Quality Advisory Committee, in collaboration with the Canadian Stroke Consortium

Table 1C: Summary Table for Selected Pharmacotherapy for Post-Stroke Depression

This table provides a summary of the pharmacotherapeutic properties, side effects, drug interactions and other important information on selected classes of medications available for use in Canada and more commonly recommended for 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, patient preference and/or past experience, side effects, and drug interactions 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 *recommended	*citalopram – Celexa *escitalopram – Cipralex fluoxetine – Prozac fluvoxamine – Luvox paroxetine – Paxil *sertraline – Zoloft	*duloxetine – Cymbalta *venlafaxine – Effexor	methylphenidate – Ritalin (amphetamine) nortriptyline – Aventyl (tricyclic antidepressant) trazodone – Desyrel (tetracylic antidepressant) *mirtazapine – Remeron (NASSA, noradrenaline and specific serotonin antagonist)
Contra-indications	concurrent monoamine oxidase inhibitor (MAOI) use	concurrent monoamine oxidase inhibitor (MAOI) use	nortriptyline – cardiac conduction abnormalities, uncontrolled narrow angle glaucoma, or concurrent monoamine oxidase inhibitor (MAOI) use
Side Effects	Serotonin syndrome, sedation (fluvoxamine, paroxetine), bleeding, and hyponatremia Fluoxetine, fluvoxamine, paroxetine: interact with certain cardiac medication e.g. clopidogrel and beta-blockers Generally reported: dry mouth, loss of appetite and weight-loss, nausea, dizziness, loss of libido, constipation or diarrhea, insomnia or somnolence, sweating	Increases in heart rate, hypertension (venlafaxine), serotonin syndrome Generally reported: dry mouth, loss of appetite and weight-loss, loss of libido, constipation, nausea, insomnia, dizziness anxiety, sweating	nortriptyline – potential effects on cognition and may increase risk of delirium (anticholinergic); 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
Landmark Trials	citalopram[6,14], fluvoxamine[8] , fluoxetine[1-5] sertraline[7,14] paroxetine[9]	reboxetine[10] , milnacipran[11], venlafaxine[12] , duloxetine[14]	trazodone[15,16] , nortriptyline[17,18] methylphenidate[19]

	Selective Serotonin Reuptake Inhibitors (SSRI)	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Other
Inclusion 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. 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: 10 – 40mg/day[6,10,14,20, 21] Maximum doses: 40mg/day adults, 20mg/day geriatric[22] escitalopram: 10 – 20mg/day Maximum doses: 20 mg/day adults,10 mg/day geriatric[22] sertraline: 50 - 200mg/day[14]	venlafaxine: 75 – 150 mg/day duloxetine: 60 – 120mg/day	trazodone: 200 – 300mg/day mirtazapine: 30mg/day nortriptyline: 20 – 100mg/day
Summary of Findings	Level 1 RCT evidence supports the efficacy of SSRIs fluoxetine and citalopram for treatment of moderate to severe post-stroke depression.	Studies were open-label or uncontrolled; no level 1 RCT evidence available to support efficacy of SNRI for treatment of post-stroke depression.	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 effective in prophylaxis Mortality & PSD: increased survival of depressed and non-depressed treated with fluoxetine or nortriptyline over placebo in 9-year follow-up[23]. Cognitive function: maintenance of executive function compared to placebo over 21 months	Anxiety in PSD: duloxetine more effective than citalopram in treating anxiety symptoms Alexithymia: venlafaxine results in greater improvement of emotional awareness than fluoxetine	Prevention of PSD: mirtazapine efficacious in preventing PSD[32] Mortality & PSD: increased survival of depressed and non-depressed treated with fluoxetine or nortriptyline over placebo in 9-year follow-up[23] Functional status (ADLs): trazodone treatment resulted in trending improvement

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	follow-up[24]; improvement in verbal and visual memory[25] Sleep: fluvoxamine improved sleep disturbances as measured by peripheral melatonin blood levels. Functional status: **fluoxetine** associated with improved motor recovery (FLAME trial)[25] Other: fluoxetine improved quality of life[2]		
Safety All antidepressants have Health Canada Warnings regarding increased risk of suicidal thinking and behavior (particularly in children, adolescents and young adults)	Discontinuation: Discontinuation of escitalopram may increase post stroke depressive symptoms over 6 months[26] 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.[27] SSRIs lower risk of cardiovascular events but increase bleeding and mortality. [28] Potential risk of hemorrhagic stroke with SSRIs[29] Delirium : anticholinergic effects (paroxetine) may play role in delirium in acute stroke patients[30] QTc prolongation: Health Canada warnings regarding citalopram. Minimal QT effect with escitalopram and sertraline. Fluvoxamine, fluoxetine and paroxetine minimal concern. [31]	QTc prolongation: Among SNRIs, venlafaxine has the greatest risk [31]	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

	Selective Serotonin Reuptake Inhibitors (SSRI)	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Other
Cost/ coverage in Canada	citalopram (20mg) $0.13 escitalopram (10mg) 0.31 and (20mg) $0.33 fluoxetine (20mg) $0.33 paroxetine (20mg) $0.33 and (30mg) $0.35 sertraline (25mg) $0.15, (50mg) $0.30 and (100mg) $0.33 fluvoxamine (50mg) $0.21 and (100mg) $0.38	duloxetine (30mg) $0.48 and (60mg) $0.98 milnacipran – not available reboxetine – not readily available, not covered by provincial drug coverage plans venlafaxine (37.5mg) $0.09, (75mg) $0.18 and (150mg) $0.19	methylphenidate (10-80mg) $0.76-$4.62 trazodone (50mg) $0.05, (100mg) ~$0.10, and (150mg) $0.15 nortriptyline (10mg) $0.26 and (25mg) $0.52 mirtazapine (15mg) ~$0.10 (30mg) ~$0.20 and (45mg) $0.29

References for Table 1C

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