Fluoxetine - MCC Standardised Package Insert vs Originator and International References

	Standardised PI	ok Prozac RSA	ok FDA NDA Prozac	ok EMEA (SPC) Fluoxetine	ok Canada	ok TGA	
1. INDICATIONS							**Indications**
Major depressive disorders	x	x	x	x	x	x	Mean of p values=Overall p value100+100+100+100+66÷5=0.93
Obsessive-compulsive disorder	x	x	x	x	x	x	
Bulimia nervosa	x	x	x	x	x	N	q=1-0.93=0.07
Total	3	3	3	3	3	2	Std Deviation=√(pq÷n)=√(0.065÷5)=√0.013=0.11
p= proportion		p=3/3=100	p=3/3=100	p=3/3=100	p=3/3=100	p=2/3=66	95% CI = p±(2.776xStd Dev) = p±(2.776x0.11)=0.31
							95%CI = 0.93±0.31 ie. 1.24 to 0.62
2. RECOMMENDED DOSAGE							**Dosage**
Safety/efficay in children not established	x	x	N	N	x	x	
Can be given with or without food	x	x	N	x	N	N	Mean of p values=Overall p value 50+60+50+80+60÷5=0.60
Avoid use of alcohol	x	N	N	N	N	N	
Lower dose or less frequent dosing in pts with intercurrent illnesses or hepatic impairment	x	N	x	x	x	x	q=1-0.60=0.40
Major depressive disorders: 20 mg daily, preferably in morning	x	x	x	N	x	x	Std Deviation=√(pq÷n)=√(0.24÷5)=√0.05=0.22
Obsessive-compulsive disorder: 20-60 mg daily	x	x	x	x	x	x	95% CI = p±(2.776xStd Dev) = p±(2.776x0.22)=0.61
Bulimia nervosa: 60 mg daily	x	x	x	x	x	N	95%CI = 0.60±0.61 ie. 1.21 to - 0.02
Upward titration over several weeks due to p'kinetic properties	x	N	x	N	x	x	
Doses > 80 mg not recommended for any indication	x	N	x	x	x	x	
Caution in elderly pts: doses > 20 mg not recommended	x	N	N	N	x	N	
Total	10	5	6	5	8	6	
p= proportion		p=5/10=50	p=6/10=60	p=5/10=50	p=8/10=80	p=6/10=60	
3. CAUTIONS							
Warnings							**Warnings**
Serotonin syndrome with fluoxetine alone or in temporal association with MAOI	x	N	N	N	x	N	
Discontinue if pts develop rash or other allergic reactions	x	x	x	x	x	x	
Anaphylactoid and serious systemic events involv skin, liver or lung	x	N	x	N	x	x	
Worsening of major depressive disorder & suicidal ideation/behavior, may/may not be causal wrt fluoxetine	x	N	N	N	x	x	
Observe pts closely for clinical worsening/suicidality at initiation & dose change	x	N	N	N	x	x	
Take same precautions taken for major depressive disorder for other psychiatric/non-psychiatric disorders	x	N	N	N	N	x	
Observed with antidepressants for major depressive disorder & psychiatric/non-psychiatric indications: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania and mania - may require change to therapeutic regimen	x	N	N	N	x	x	
Taper dosage when discontinuing fluoxetine	x	N	N	N	x	N	
Total	8	1	2	1	7	6	
p= proportion		p=1/8=13	p=2/8=25	p=1/8=0.13	p=7/8=88	p=6/8=75	
Pregnancy & Lactation							
Safety in pregnancy & lactation not established	x	x	x	N	x	x	
Contra-indications							**Pregnancy Lactation Contra-Indications**
Hypersensitivity to fluoxetine or any of the ingredients	x	x	x	x	x	x	
Concomitant MAOI's 14 days after disc MAOI, 5 weeks after stopping fluoxetine	x	x	x	x	x	x	
Severe renal function impairment (GFR < 10 ml/min)	x	x	N	N	N	N	
Total	4	4	3	2	3	3	
p= proportion		p=4/4=100	p=3/4=0.75	p=2/3=67	p=3/4=0.75	p=3/4=75	

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Special precautions							Special precautions
Close monitoring in first 1-2weeks as improvement may not occur	x	x	N	x	x	x	
Close supervision of high risk patients eg. Suicidal tendencies	x	x	x	x	x	x	
Same precautions as for pts with obsessive-compulsive disorder	x	x	x	N	x	N	
History of seizures due to increased risk of seizures	x	N	x	x	x	x	
Discontinue if pt develops a seizure	x	x	N	x	N	N	
Avoid in unstable epilepsy	x	x	N	x	N	N	
Careful monitoring of pts with controlled epilepsy	x	x	N	x	N	N	
Prolonged seizures in ECT	x	x	N	x	x	x	
Delayed fluoxetine metabolism in impaired hepatic function	x	N	x	x	x	x	
Lower doses/less frequent dosing with significant hepatic impairment	x	x	x	x	x	x	
Accumulation of metabolites in renal function impairment	x	N	N	N	N	x	
Dose adjustment in mild to moderate renal failure (GFR 10-50 ml/min)	x	x	N	N	N	N	
Underweight individuals - weight loss	x	x	x	x	x	x	
Diabetes mellitus - altered glycaemic control	x	x	x	x	x	x	
Abnormal bleeding in pts with history of bleeding disorders	x	x	x	x	x	x	
							Mean of p values=Overall p value 0.61+0.48+0.52+0.71+0.71÷5=0.61
Extrapyramidal symptoms and aggravation of Parkinson's disease in pts with extrapyramidal disorders	x	N	N	N	N	N	
Acute cardiac disease - limited clinical experience	x	x	x	x	x	x	q=1-0.61=0.39
Impairment of mental alertness or physical co-ordination eg. Operating machinery, driving motor vehicle, perform potentially hazardous tasks	x	x	x	N	N	x	pq=0.39x0.61=0.24 Std Deviation=√(pq÷n)=√(0.24÷5)=√0.05=0.22
Withdrawal symptoms - dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, agitation, anxiety, nausea	x	N	N	N	x	x	95% CI = p±(2.776xStd Dev) = p±(2.776x0.22)=p±0.61 95%CI = 0.61±1.205 ie. 1.22 to 0
Total	19	14	10	13	12	13	
p= proportion		p=14/19=74	p=10/19=0.53	p=13/19=68	p=12/19=63	13/19=68	
Total Cautions	31	19	15	16	22	16	
p= proportion		p=19/31=0.61	p=15/31=0.48	16/31=0.52	p=22/31=0.71	p=22/31=0.71	

4. SIDE EFFECTS							Side Effects
Palpitations	x	x	x	N	x	x	
Headache	x	x	x	x	x	x	
Nervousness	x	x	x	x	x	x	
Anxiety	x	x	x	x	x	x	
Drowsiness	x	x	x	x	x	N	
Fatigue	x	x	N	x	x	N	
Insomnia	x	x	x	x	x	x	
Tremor	x	x	x	x	x	x	
Asthenia	x	x	x	N	x	x	
Dizziness	x	x	x	x	x	x	
Abnormal dreams	x	x	x	x	x	x	
Agitation	x	x	x	x	x	N	
Seizures	x	x	N	x	x	x	
Hypomania	x	x	N	N	N	N	
Mania	x	x	N	x	N	x	
Dyskinesias	x	x	N	N	x	N	
Weight loss	x	N	x	N	x	x	
Hyponatraemia	x	x	N	x	N	N	
Hypothyroidism	x	N	x	N	x	N	
Fever	x	x	x	N	x	N	
Nausea	x	x	x	x	x	x	
Diarrhoea	x	x	x	x	x	x	
Dyspepsia	x	x	x	x	x	x	
Anorexia	x	x	x	N	x	x	
Vomiting	x	x	x	x	x	x	
Dry mouth	x	x	x	x	x	x	
Decreased libido	x	x	x	N	x	x	
Sexual dysfunction (delayed/inhibited orgasm)	x	x	x	x	x	x	
Raised tranaminase levels	x	x	x	x	x	N	
Arthralgia	x	N	x	x	x	N	
Myalgia	x	N	x	x	x	N	
Visual disturbances	x	x	x	x	x	x	
Dyspnoea	x	x	N	x	N	N	
Pulmonary inflammation and/or fibrosis	x	x	N	x	N	N	
Rash	x	x	x	x	x	x	
Urticaria	x	x	N	x	N	x	
Prutitus	x	N	x	x	x	x	
Excessive sweating	x	x	x	x	x	x	
Anaphylactoid reactions	x	x	N	x	N	x	

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Serum sickness	x	x	N	x	N	x	
Aplastic anaemia	x	x	N	N	N	N	
Cerebral vascular accident	x	x	x	N	x	N	
Confusion	x	x	x	x	x	N	
Ecchymoses	x	x	N	x	N	x	
Eosinophilic pneumonia	x	x	N	N	N	N	
Gastro-intestinal haemorrhage	x	x	x	x	x	N	
Hyperprolactinaemia	x	x	x	x	N	N	
Neuroleptic malignant syndrome-like events	x	x	x	N	x	x	
Pancreatitis	x	x	x	N	x	N	Mean of p values=Overall p value 0.91+0.70+0.66+0.79+0.54÷5=0.72
Suicidal ideation	x	x	x	N	x	N	
Pancytopenia	x	x	N	N	x	N	q=1-0.72=0.28
Thrombocytopenia	x	x	x	N	x	N	pq=0.72x0.28=0.20
Purpura	x	x	x	x	x	x	Std Deviation=√(pq÷n)=√(0.20÷5)=√0.04=0.20
Immune-related haemolytic anaemia	x	x	N	N	x	N	95% CI = p±(2.776xStd Dev) = p±(2.776x0.20)=p±0.56
Vaginal bleeding after fluoxetine withdrawal	x	x	x	x	x	N	95%CI = 0.72±0.56 ie. 1.28 to 0.16
Violent behaviour	x	x	N	N	x	N	
Total	56	51	39	37	44	30	
p= proportion		P=51/56=91	p=39/56=70	p=37/56=66	p=44/56=79	p=30/56=54	

5. DRUG INTERACTIONS							
Long elimination half life fluoxetine & norfluoxetine gives potential for drug interactions for several weeks after discontinuation	x	x	N	x	N	N	
MAOI's	x	x	x	x	x	x	
Reduce dose of medicines metabolised by CYP P450 CYP2D6 with narrow therapeutic index, fluoxetine inhibits CYP2D6	x	N	x	x	x	x	Mean of p values=Overall p value 0.67+0.78+0.67+0.89+0.89=÷3=0.78
Lithium incr & decr in serum conc - monitor litium levels	x	x	x	x	x	x	q=1-0.78=0.22 pq=0.78x0.22=0.17
Phenytoin, carbamazepine, haloperidol, clozapine, diazepam, alprazolam, imipramine, desimipramine - changes in blood levels & poss toxicity	x	N	N	N	x	x	Std Deviation=√(pq÷n)=√(0.17÷5)=√0.03=0.18
Half life of diazepam prolonged	x	x	x	N	x	x	95% CI = p±(2.776xStd Dev) = p±(2.776x0.18)=p±0.50
Tryptophan - agitation, restlessness & GIT distress	x	x	x	x	x	x	95%CI = 0.78±0.50 ie. 1.28 to 0.28
Alteration of plasma conc of other protein bound medicines eg. Warfarin, digoxin	x	x	x	N	x	x	
Altered anti-coagulant effects & increased bleeding with warfarin. Monitor coagulation when stopping fluoxetine	x	N	x	x	x	x	
Total	9	6	7	6	8	8	
p= proportion		P=6/9=67	p=7/9=78	p=6/9=67	p=8/9=0.89	p=8/9=89	