Comparison of First-Line Medications Recommended to Treat Depression and/or Anxiety in Individuals with CF ages 12-Adulthood

	CITALOPRAM	**ESCITALOPRAM**	**FLUOXETINE**	**SERTRALINE**
BASIC CHARACTERISTICS				
Neurochemical class	SSRI	SSRI; active *S*-isomer of citalopram	SSRI	SSRI
Selected trade names	--Akarin --Celexa --Cipramil	--Cipralex --Lexapro --Seroplex	--Adofen --Sarafem --Fluctine --Prozac	--Gladem --Lustral --Zoloft
	CITALOPRAM	**ESCITALOPRAM**	**FLUOXETINE**	**SERTRALINE**
DOSAGE FORMS	Tablets: 10, 20, & 40 mg Oral Solution: 10 mg/5 ml	Tablets: 5, 10, & 20 mg Oral Solution: 5 mg/5 ml	Prozac: Capsules: 10, 20, & 40 mg Weekly Capsule: 90 mg Oral Solution: 20 mg/5 ml Sarafem: (PDD Only) Tablets: 10, 20, & 60 mg	Tablets: 25, 50, & 100 mg Oral Concentrate: 20 mg/ml
DOSING				
Reduced starting dose --For pediatric or medically complex individuals	Start at 5-10 mg/day	Start at 2.5-5 mg/day	Start at 5-10 mg/day	Start at 12.5-25 mg/day
Dose increase --Assess clinical reponse, considering repeat GAD-7 and/or PHQ-9 and functional improvement --Assess adherence to medication --If symptoms persist and side effects are tolerable, consider dose increase	Increase by 5-10 mg every 1-4 weeks if needed	Increase by 2.5-5 mg every 1-4 weeks if needed	Increase by 5-10 mg every 1-4 weeks if needed	Increase by12.5-25 mg every 1-4 weeks if needed
Typical target dose --To minimize the risk of relapse, consider continuing SSRI for one year following an episode of treatment before tapering gradually --Patients with recurrent symptoms may need longer-term treatment	20-40 mg/day	10-20 mg/day	20-60 mg/day	50-200 mg/day

Adapted from Quittner AL, et al. *Thorax* 2016;71:26-34

Elevated dose (off-label) --High doses may be required in cases of partial response, poor absorption, enhanced hepatic metabolism, CYP genetic polymorphism, drug-drug interaction --Consider change in SSRI or referral for specialized consultation	Up to 80 mg/day	Up to 40 mg/day	Up to 80 mg/day	Up to 250 mg/day
Dose adjustment for renal impairment	None (Caution if eGFR <20 ml/min)	None (Caution if eGFR <20 ml/min)	None	Consider reducing maximum dose in severe renal impairment
Dose adjustment for hepatic impairment	Maximum 20 mg/day	Maximum 10 mg/day	Reduce dose (50% reduction in severe hepatic impairment)	Reduce dose
TDM target blood level (ng/ml) --TDM is not routinely used for SSRIs --Consider TDM when elevated doses are required, or drug-drug interactions or CYP genetic polymorphisms are suspected	50-110	15-80	120-500	10-150
	CITALOPRAM	**ESCITALOPRAM**	**FLUOXETINE**	**SERTRALINE**
DRUG-DRUG INTERACTIONS				
CYP metabolism of SSRI	Major substrates: 2C19 3A4 Minor substrates: 2D6	Major substrates: 2C19 3A4 Minor substrates: 2D6	Major substrates: 2C9 2D6* *metabolite norfluoxetine is exclusive substrate of CYP2D6, increasing clinical significance Minor substrates: 1A2 2B6 2C19 3E1 3A4	Major substrates: None Minor substrates: 2B6 2C9 2D6 2C19 3A4

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Inhibition of CYP by SSRI	Weak to moderate inhibitor of: 2D6	Weak to moderate inhibitor of: 2D6	Strong inhibitor of: 2D6 Weak to moderate inhibitor of: 1A2 2B6 2C9 2C19 3A4	Weak to moderate inhibitor of: 1A2 2B6 2C9 2C19 2D6 3A4
Selected CYP-mediated drug-drug interactions: Medications commonly used in CF that may require dose reduction of SSRI or of CF medication	2C19 inhibitors: Cimetidine Fluconazole Esomeprazole Omeprazole Voriconazole 3A4 inhibitors: Clarithromycin Itraconazole Ketoconazole Voriconazole Posaconazole Fluconazole Erythromycin Ivacaftor (weak) 3A4 inducers: Lumacaftor Rifampin 3A4 substrate: Ivacaftor	2C19 inhibitors: Cimetidine Fluconazole Esomeprazole Omeprazole Voriconazole 3A4 inhibitors: Clarithromycin Itraconazole Ketoconazole Voriconazole Posaconazole Fluconazole Erythromycin Ivacaftor (weak) 3A4 inducers: Lumacaftor Rifampin 3A4 substrate: Ivacaftor	2C9 inhibitors: Fluconazole Miconazole 2D6 inhibitors: Cimetidine Methadone Metoclopramide 2D6 substrates: Dextromethorphan Hydroxycodone Ondansetron Morphine Codeine* Tramadol* *analgesic effect may be reduced by 2D6 inhibition	2C19 inhibitors: Cimetidine Fluconazole Esomeprazole Omeprazole Voriconazole 3A4 inhibitors: Clarithromycin Itraconazole Ketoconazole Voriconazole Posaconazole Fluconazole Erythromycin Ivacaftor (weak) 3A4 inducers: Lumacaftor Rifampin 3A4 substrate: Ivacaftor
QTc prolongation --Modest dose-dependent increases in QTc are unlikely to be clinically significant unless QTc is high (>500 ms) --May consider EKG monitoring when used with other medications	Carries FDA warning: http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm --Discontinue use if QTc>500 ms persistently --Correct hypokalemia,	Less likely	Less likely	Less likely

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that prolong QTc: • Antifungals: fluconazole, ketoconazole • Macrolides: erythromycin, clarithromycin, azithromycin • Methadone • Quinolones: levofloxacin, moxifloxacin	hypomagnesemia			
Serotonin syndrome --Potentially fatal syndrome includes change in mental status; autonomic instability (sweating, tachycardia, fever); tremor, myoclonus, hyperreflexia; abdominal pain and diarrhea --Relative contraindication of SSRI use with linezolid; when alternatives are unavailable, use with informed consent and clinical monitoring	linezolid	linezolid	linezolid	linezolid
ADVERSE EFFECTS				
Common SSRI side effects	--Nausea, diarrhea, sexual dysfunction, insomnia, restlessness, and headache may occur with any SSRI --May improve with time, slower dose titration, dose reduction, or change in medication --Insufficient evidence exists regarding effects of SSRIs in CF on bone density, hemoptysis, or weight gain			
Suicidal thoughts and/or behaviors	--Depression and anxiety can themselves be associated with suicidal thoughts and/or behavior --Concerns have been raised regarding increased risk of suicidal thoughts and/or behavior with the use of antidepressant medications, particularly when starting medication in pediatric and young adult patients --The risk/benefit ratio remains in favor of using SSRIs when clinically appropriate --Regardless of treatment modality, good clinical practice supports ongoing surveillance of suicidal thoughts in order to properly intervene, particularly at times of higher stress or when initiating or changing treatment			
SSRI discontinuation syndrome	--When discontinuing an SSRI, taper down gradually whenever possible to avoid discontinuation symptoms --May include nausea, headache, dizziness, paresthesias, and insomnia --Fluoxetine is least likely to cause discontinuation syndrome due to its longer half-life			

CF: Cystic fibrosis
CYP: Cytochrome P450 isoenzyme

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EKG: Electrocardiogram
GAD-7: Generalized Anxiety Disorder-7 (anxiety rating scale)
FDA: United States Food and Drug Administration
PHQ-9: Patient Health Questionnaire-9 (depression rating scale)
SSRI: Selective serotonin reuptake inhibitor
TDM: Therapeutic drug monitoring
QTc: Corrected QT interval on EKG

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