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Clinical Pearls to Manage Schizophrenia

A Quick Reference Guide

VA Academic Detailing Service

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Real Patient Results

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Real Provider Resources

Real Patient Results

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PharmacyAcademicDetailingProgram@va.gov

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https://vaww.portal2.va.gov/sites/ad

Psychosocial Interventions for Patients with Schizophrenia[1]	
Intervention	**Description**
Cognitive Behavioral Therapy	Addresses inaccurate or negative thought patterns that underlie emotional responses and maladaptive behavioral patterns. Includes the development of specific cognitive and behavioral strategies to cope with symptoms. Should be offered as adjunct for patients with persistent psychotic symptoms despite adequate pharmacotherapy. Duration approximately 4–9 months.
Skills Training	Skills needed for everyday activities in order to improve social interactions and independent living. E.g. communication skills: having a casual conversation, making friends, expressing feelings, or obtaining something from another person.
Supported Employment	Individually tailored job development, searching for a job, the availability of ongoing job supports, and the integration of vocational and mental health services.
Assertive Community Treatment	Especially helpful for patients who are at risk of repeated hospitalization or have recent homelessness. Key elements include outreach to patients in the community, low patient to staff ratios and high frequency of patient contact. Services should be provided directly by a multi-disciplinary team including a prescriber.

continued

Psychosocial Interventions for Patients with Schizophrenia[1]	
Intervention	**Description**
Psychosocial Interventions For Substance Use Disorders	Motivational enhancement and behavioral strategies that focus on engagement in treatment, coping skills training, relapse prevention training, and its delivery in a service model that is integrated with mental health care. Should be offered to patients with schizophrenia and comorbid alcohol or drug use disorders.
Family-Based Services	Beneficial for patients who have regular contact with family members or significant others. Includes illness education, crisis intervention, emotional support, and training on how to cope with illness symptoms and related problems. Duration approximately 6–9 months.
Psychosocial Interventions For Weight Management	For patients who are overweight or obese (BMI ≥25). Psychoeducation focused on nutrition and portion control; behavioral self-management including motivational enhancement; goal setting; regular weigh-ins; self-monitoring of daily food and activity levels; and physical activity modifications. Duration of intervention is at least 3 months.
Token Economy Interventions	For long-term inpatients or those in the residential care setting. Systems of care based on the principles of operant conditioning and social learning. Utilizes contingent positive reinforcement and the avoidance of punishing consequences for clearly defined target behaviors in order to improve personal hygiene, social interactions and other adaptive behaviors.

Side Effect Profiles of Common Antipsychotic Medications[2–16]								
	Medication	Safety						
		Anti-cholinergic	EPS	QT Prolongation	Sedation	Orthostatic Hypotension	Prolactin ↑	CM Side Effects
FGA	High Potency (haloperidol)	+	++++	++	+	+	+++	+
	Moderate Potency (perphenazine)	+	+++	+	+	+	+++	+
	Moderate Potency (loxapine)	+	+++	+	++	++	+++	+
	Low Potency (chlorpromazine)	+++	+++	++	++++	++++	+++	++

CM = Cardiometabolic, EPS = Extrapyramidal Side Effects, FGA = First Generation Antipsychotic, SGA = Second Generation Antipsychotic, +/- = insignificant, + = low, ++ = moderate, +++ = moderately high, ++++ = high, **NF = Not currently on VA National Formulary for schizophrenia.**

continued

Side Effect Profiles of Common Antipsychotic Medications[2–16]								
	Medication	Safety						
		Anti-cholinergic	EPS	QT Prolongation	Sedation	Orthostatic Hypotension	Prolactin↑	CM Side Effects
SGA	Asenapine (NF)	+/-	+	+	+	+	+/-	+
	Aripiprazole	+/-	+	+/-	+	+/-	+/-	+
	Brexpiprazole (NF)	+	+	+/-	+	+/-	+/-	++
	Cariprazine (NF)	+/-	+++	+/-	+	+/-	+/-	+
	Clozapine	++++	+/-	+	++++	++++	+/-	++++
	Iloperidone (NF)	+/-	+	++	+	+++	+	++

CM = Cardiometabolic, EPS = Extrapyramidal Side Effects, FGA = First Generation Antipsychotic, SGA = Second Generation Antipsychotic, +/- = insignificant, + = low, ++ = moderate, +++ = moderately high, ++++ = high, **NF = Not currently on VA National Formulary for schizophrenia.**

continued

Side Effect Profiles of Common Antipsychotic Medications[2–16]								
	Medication	Safety						
		Anti-cholinergic	EPS	QT Prolongation	Sedation	Orthostatic Hypotension	Prolactin ⬆	CM Side Effects
SGA	Lurasidone **(NF)**	+/-	++	+/-	+	++	+	+
	Olanzapine	++	++	+	++	++	+/-	++++
	Paliperidone **(NF-Oral)**	+	++	+	+	++	++++	++
	Quetiapine	+	+/-	++	+++	++	+/-	+++
	Risperidone	+	++	+	+	++	++++	++
	Ziprasidone	+/-	++	++	+	++	+	+/-

CM = Cardiometabolic, EPS = Extrapyramidal Side Effects, FGA = First Generation Antipsychotic, SGA = Second Generation Antipsychotic, +/- = insignificant, + = low, ++ = moderate, +++ = moderately high, ++++ = high, **NF = Not currently on VA National Formulary for schizophrenia.**

Summary of Atypical Antipsychotic Cardiometabolic Side Effects [2–16]				
Medication	**Metabolic Syndrome**	**Weight Gain**	**Glucose Dysregulation**	**Dyslipidemia**
Aripiprazole	+	+	++	+
Asenapine **(NF)**	+	+	+	+
Brexpiprazole **(NF)**	++	++	++	++
Cariprazine **(NF)**	+	+++	+	+
Clozapine	++++	++++	++++	++++
Iloperidone **(NF)**	++	++	+	+
Lurasidone **(NF)**	+	+	++	+
Olanzapine	++++	++++	++++	++++
Paliperidone **(NF-Oral)**	++	++	+++	++
Quetiapine	+++	+++	+++	+++
Risperidone	++	++	+++	++
Ziprasidone	-/+	+	-/+	-/+

+/- = insignificant, + = low, ++ = moderate, +++ = moderately high, ++++ = high, *Newer antipsychotic medications do not have enough data to truly assess their effects on metabolic parameters and ratings are based on 6-week clinical trial data. Data indicates that treatment naive patients gain weight even on low risk medications, **NF = Not currently on VA National Formulary for schizophrenia.**

Recommended Cardiometabolic Monitoring[4]						
	Baseline	4 Weeks	8 Weeks	12 Weeks	6 Months	Yearly
Medical History	X					X
Weight	X	X	X	X	X	X
Blood Pressure	X			X		X
HgA1c or Fasting Plasma Glucose	X			X		X
Fasting Lipids	X			X		X

More frequent monitoring should be conducted for those who have gained more than 5% of their body weight

Long-Acting Injectable Antipsychotics (LAI)[17–29]										
LAI	Supplied	Formulation	Injection Site and Technique	Overlap with Oral	Loading Dose Possible	Dose Range (mg)	Max Dose (mg)	Dosing Interval (weeks)	Time to Peak	Time to Steady State
Fluphenazine decanoate (Prolixin Decanoate®)	25 mg/mL	ester in sesame seed oil	deltoid or gluteal region Z track	2 week	No	12.5–100	100 mg every 2 weeks	2–4	8–24 hours	2–3 months
Haloperidol decanoate (Haldol® Decanoate)	50 mg/mL 100 mg/mL	ester in sesame seed oil	deltoid or gluteal region Z track	1 to 3 months (none if loading)	Yes	20–450	450 mg every 4 weeks	4	3–9 days	2–3 months
Risperidone microspheres (Risperdal® Consta®)	12.5 mg 25 mg 37.5 mg 50 mg	microsphere matrix in aqueous suspension	deltoid or gluteal region Standard	3–6 weeks	No	12.5–50	50 mg every 2 weeks	2	4–5 weeks	6–8 weeks
Paliperidone palmitate (Invega® Sustenna™)	39 mg 78 mg 117 mg 156 mg 234 mg	nanoparticles in aqueous suspension	deltoid only (loading dose) deltoid or gluteal (maintenance) Standard	none	Yes	39–234	234 mg every 4 weeks	4	13 days	5–6 weeks

continued

Long-Acting Injectable Antipsychotics (LAI)[17–29]										
LAI	**Supplied**	**Formulation**	**Injection Site and Technique**	**Overlap with Oral**	**Loading Dose Possible**	**Dose Range (mg)**	**Max Dose (mg)**	**Dosing Interval (weeks)**	**Time to Peak**	**Time to Steady State**
Olanzapine pamoate **(NF)** (Zyprexa® Relprevv™)	210 mg 300 mg 405 mg	nanoparticles in aqueous suspension	gluteal region only Standard	none	No	150–405	300 mg every 2weeks or 405 mg every 4 weeks	2–4	<1 week	3 months
Aripiprazole ER (Abilify Maintena™)	300 mg 400 mg	low solubility particles in aqueous suspension	gluteal region only Standard	2 weeks	No	200–400	400 mg every 4 weeks	4	5–7 days	3–4 months
Aripiprazole lauroxil **(NF)** (Aristada™)	441 mg 662 mg 882 mg	aqueous suspension	deltoid (441 mg dose only) or gluteal (441 mg, 662 mg or 882 mg)	21 days	No	441-882	882 mg every 4 weeks	4 882 mg 4-6	4 days	4 months

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Conversion from Oral Tablets to Long Acting Injectable (LAI)[17–29]				
Fluphenazine decanoate (Prolixin Decanoate®) 1 mg oral = 1.25 mg LAI May be given subcutaneously. Considerable patient variability.	**Day 1:** 12.5 mg LAI + 10 mg oral for 2–3 days	**Day 3 or 4:** ⬇ oral dose by 50% (5 mg oral for 2–3 days)	**Day 6 or 7:** ⬇ oral dose by 50% (2.5 mg oral for 2–3 days)	**Day 15:** Fluphenazine decanoate 12.5 mg Discontinue oral Make adjustments based on clinical response if needed
Haloperidol decanoate (Haldol® Decanoate) 20x oral = Loading LAI dose 10–20x oral = Target LAI dose Max volume per injection = 3 mL	**Day 1:** Haloperidol decanoate 50-100 mg (max loading dose = 100 mg) May give 10 mg oral daily x 7 days	**Day 3–7:** Complete loading dose	**4 weeks after 2nd LAI:** May need to ⬇ by 25% to prevent excess drug accumulation	**4 weeks after 3rd LAI:** May need to ⬇ by 25% to achieve maintenance dose

continued

Conversion from Oral Tablets to Long Acting Injectable (LAI)[17–29]					
Risperidone microspheres (Risperdal® Consta®)	**1–2 mg oral:** 12.5 mg LAI	**2 mg oral:** 25 mg LAI	**3–4 mg oral:** 37.5 mg LAI	**5–6 mg oral:** 50 mg LAI	
	+ Oral for 3 weeks and gradually begin to taper off at week 4. Oral dosage should be stopped within 6 weeks. Refrigerate and use within 6 hours of suspension				
Paliperidone palmitate (Invega® Sustenna™) 9–hydroxyrisperidone Pre-filled syringes May need to continue oral risperidone during initial 8 days	**1–2 mg oral**: 39 mg LAI	**2 mg oral:** 78 mg LAI	**3–4 mg oral**: 117 mg LAI	**5–6 mg oral:** 156 mg LAI	**12 mg oral:** 234 mg LAI
	CrCl >80	**Day 1**: 234 mg	**Day 8**: 156 mg	**Maintenance**: equivalent dose (39–234 mg)	
	CrCl 50–80	**Day 1**: 156 mg	**Day 8**: 117 mg	**Maintenance**: 78 mg	
	CrCl <50	DO NOT USE			
Olanzapine pamoate **(NF)** (Zyprexa® Relprevv™) Must enroll in national registry due to risk of post-injection delirium sedation syndrome	**10 mg PO**: 210 mg LAI every 2 weeks **OR** 405 mg LAI every 4 weeks for first 8 weeks, then 150 mg LAI every 2 weeks **OR** 300 mg LAI every 4 weeks				
	15 mg PO: 300 mg LAI every 2 weeks for first 8 weeks, then 210 mg LAI every 2 weeks **OR** 405 mg LAI every 4 weeks				
	20 mg PO: 300 mg LAI every 2 weeks				

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continued

Conversion from Oral Tablets to Long Acting Injectable (LAI)[17–29]

Aripiprazole ER (Abilify Maintena™) Must be reconstituted	**Day 1:** 400 mg LAI + 10-20 mg oral	**Day 2–14:** 10–20 mg oral daily	**Day 15:** Discontinue oral	**4 weeks after 1st LAI:** 400 mg LAI or ⬇ to 300 mg for tolerability
CYP450 dose adjustments	**Dose Adjustments for Drug Interactions** **Patient taking 400 mg:** • Strong CYP2D6 **or** CYP3A4 inhibitors: 300 mg • CYP2D6 **and** CYP3A4 inhibitors: 200 mg • CYP3A4 inducers: Avoid use **Patient taking 300 mg:** • Strong 2D6 **or** CYP3A4 inhibitors: 200 mg • CYP2D6 **and** CYP3A4 inhibitors: 160 mg • CYP3A4 inducers: Avoid use			
Aripiprazole lauroxil **(NF)** (Aristada™)	10 mg oral: 441mg LAI	15 mg oral: 662 mg LAI	≥20 mg oral: 882 mg LAI	In conjunction with first injection, administer treatment with oral aripiprazole for 21 consecutive days
CYP450 dose adjustments	• Strong CYP 3A4 **or** strong CYP 2D6 inhibitor : use next lower strength, no dosage adjustments necessary with 441 mg LAI, if tolerated • Strong CYP 3A4 **and** strong CYP 2D6 inhibitor: avoid 662 mg and 882 mg LAI dose, no dosage adjustments necessary if taking 441 mg LAI, if tolerated • Strong CYP 3A4 inhibitor **and** poor CYP 2D6 metabolizer: reduce to 441 mg LAI, if tolerated • CYP 3A4 inducers: increase 441 mg to 662 LAI, no adjustments needed for 662 mg or 882 mg dose *Dose changes only need to be made if CYP450 modulators are added for > 2 weeks*			

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Prior to Steady State[17,24–26,29,30]			
LAI	**Avoiding Missed Doses**	**Missed Dose Prior to Steady State**	**Missed Maintenance Dose**
Fluphenazine decanoate (Prolixin Decanoate®)	Dosing every 7 days may be necessary to avoid peak plasma level adverse effects or symptom recurrence		
Risperidone microspheres (Risperdal® Consta®)		**6–8 weeks:** Provide oral supplementation when reinitiating therapy	**<6 weeks:** Administer previously stabilized dose. Oral supplementation may not be necessary **>6 weeks:** Oral supplementation should be considered
Aripiprazole ER (Abilify Maintena™)	**2nd and subsequent injections:** No sooner than 26 days after the previous injection	**>4–5 weeks after 1st or 2nd dose:** Administer as soon as possible **>5 weeks after 1st or 2nd dose:** Restart concomitant oral aripiprazole for 14 days with injection	**>4–6 weeks after 3rd or subsequent doses:** Administer as soon as possible **>6 weeks after 3rd or subsequent doses:** Restart concomitant oral aripiprazole for 14 days with the next administered injection

continued

Prior to Steady State[17,24–26,29,30]			
LAI	**Avoiding Missed Doses**	**Missed Dose Prior to Steady State**	**Missed Maintenance Dose**
Paliperidone palmitate (Invega® Sustenna™)	**2nd injection:** Administer 4 days before or after the one week time point **3rd and subsequent injections:** Administer up to 7 days before or after the monthly time point	**<4 weeks after 1st dose:** 156 mg in deltoid muscle followed by 117 mg in the deltoid or gluteal muscle 5 weeks later **4–7 weeks after 1st dose:** 156 mg in deltoid muscle followed by another 156 mg in the deltoid 1 week later **>7 weeks after 1st dose:** 234 mg in deltoid muscle followed by 156 mg 1 week later followed by monthly maintenance dose of 39–234 mg	**4–6 weeks:** Administer previously stabilized dose as soon as possible followed by injections at monthly intervals **>6 weeks to 6 months:** Resume the same dose patient was previously stabilized on unless the dose was 234 mg. If patient was on 234 mg dose, administer 156 mg in the deltoid followed by another 156 mg in the deltoid 1 week later followed by monthly injections. **>6 months:** 234 mg in deltoid followed by 156 mg in deltoid 1 week later followed by monthly maintenance dose of 39–234 mg

continued

Prior to Steady State[17,24–26,29,30]					
LAI	**Avoiding Missed Doses**	**Length of Time Since Last Injection**			
Aripiprazole lauroxil **(NF)** (Aristada™)	Oral supplementation for first 21 days required	**Dose of Last LAI**	**No Oral Supplementation Reqired**	**Supplement Oral x 7 days**	**Supplement Oral x 21 days**
		441 mg every 4 weeks	≤6 weeks	>6 and ≤7 weeks	>7 weeks
		662 mg every 4 weeks	≤8 weeks	>8 and ≤12 weeks	>12 weeks
		882 mg every 4 weeks	≤8 weeks	>8 and ≤12 weeks	>12 weeks
		882 mg every 6 weeks	≤8 weeks	>8 and ≤12 weeks	>12 weeks

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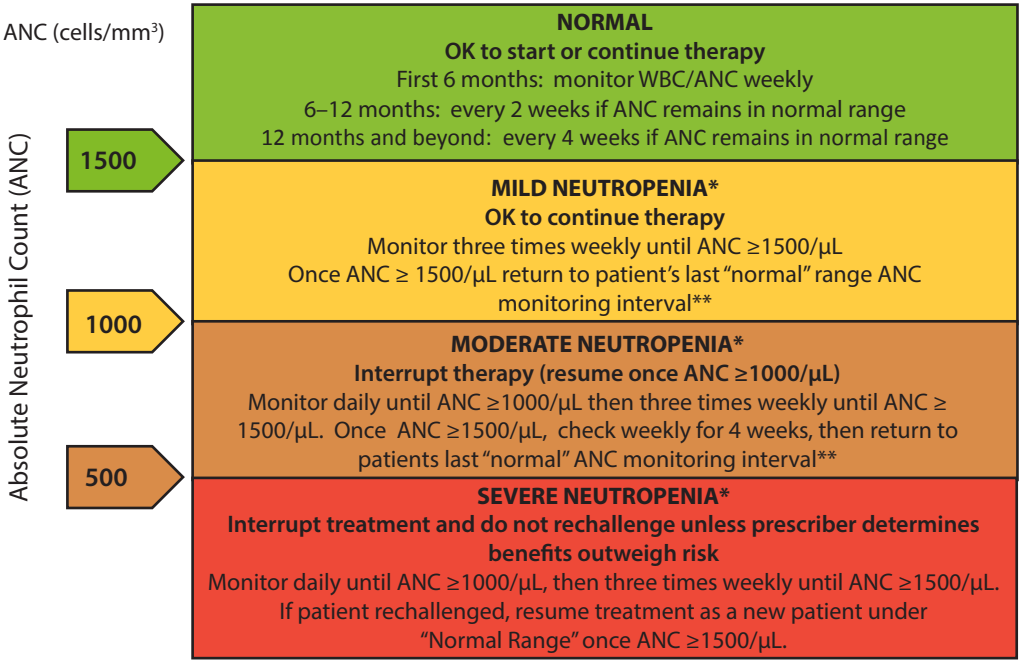
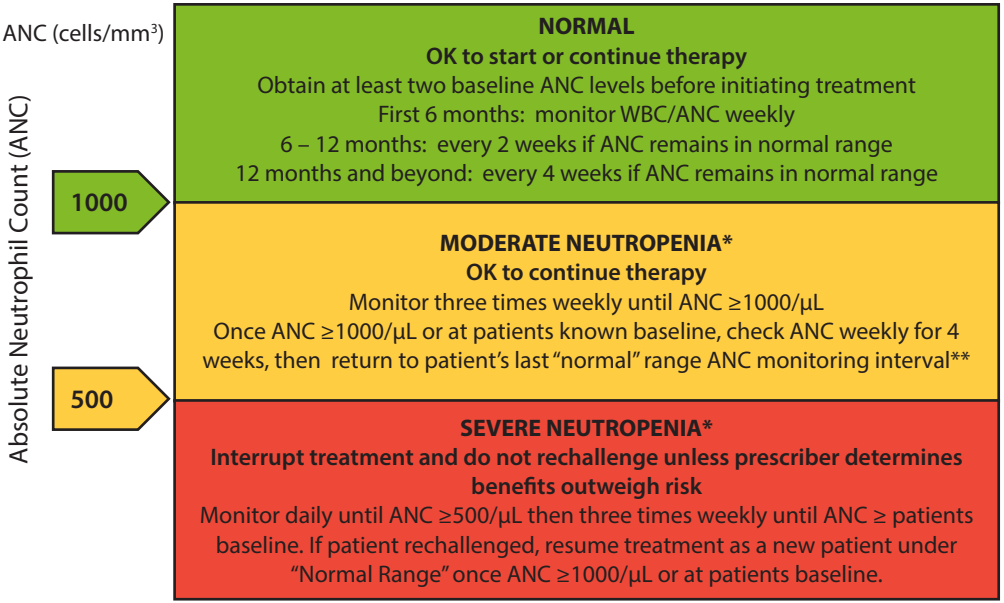
Clozapine and Frequency of Hematologic Monitoring: General Population[14]



*Confirm all initial reports of ANC less than 1500/µL with a repeat ANC within 24 hrs. ** If clinically appropriate; Hematology consultation recommended for moderate and severe neutropenia.

Clozapine and Frequency of Hematologic Monitoring: Benign Ethnic Neutropenia (BEN)[14]



*Confirm all initial reports of ANC less than 1500/µL with a repeat ANC within 24 hrs.
** If clinically appropriate; Hematology consultation recommended for moderate and severe neutropenia.

- Benign ethnic neutropenia (BEN) is a condition where ANC values are lower than "standard" laboratory ranges for neutrophils
- BEN is commonly observed in individuals of African descent (25-50%) and some Middle Eastern ethnic groups
- BEN is more common in men
- Patients with BEN have normal hematopoietic stem-cell number and myeloid maturation
- BEN patients are healthy and do not suffer for repeated or severe infections
- **They are not at increased risk for developing clozapine-induced neutropenia**
- Additional evaluation may be needed to determine if baseline neutropenia is due to BEN thus hematology consultation is recommended

General Guidelines for Management of All Patients with Fever or with Neutropenia[14]

- Fever is often the first sign of neutropenic infection
- Interrupt clozapine as a precautionary measure in patients who develop fever (38.5°C [101.3°F] or greater), and obtain an ANC level
- If fever occurs in any patient with an ANC less than 1000/µL, initiate appropriate workup and treatment for infection and follow treatment recommendations and monitoring protocols

Calculating Absolute Neutrophil Count (ANC)

ANC equals the total WBC count multiplied by the total percentage of neutrophils (segs plus bands):

$$\text{ANC} = \text{WBC (mm}^3\text{)} \times \frac{\text{(\% Neutrophils)}}{100}$$

Example:
WBC = 4.3; Segs = 48%; Bands = 2%
ANC = 4300 x (0.48 + 0.02) = 4300 x 0.5
ANC = 2150
An online ANC calculator can be found at **http://www.globalrph.com/anc.htm**

Clozapine Initiation and Titration*[14]							
Week 1	AM (mg)	PM (mg)	TOTAL (mg)	Week 2	AM (mg)	PM (mg)	TOTAL (mg)
Day 1	12.5	0–12.5	12.5–25	Day 8	50	100	150
Day 2	25	——	25	Day 9	100	100	200
Day 3	25	25	50	Day 10	100	100	200
Day 4	25	50	75	Day 11	50	200	250
Day 5	50	50	100	Day 12	50	200	250
Day 6	50	75	125	Day 13	100	200	300
Day 7	50	100	150	Day 14	100	200	300

* Titration recommendations above are guidelines only. Individual patient characteristics should be considered and dosing should be adjusted accordingly.

- Dose may be consolidated into once daily dosing.
- Subsequent dose increase should not be made more than once or twice a week; increments not to exceed 100 mg.
- Must be retitrated if not taken for >48 hrs.

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This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing SharePoint. These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

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