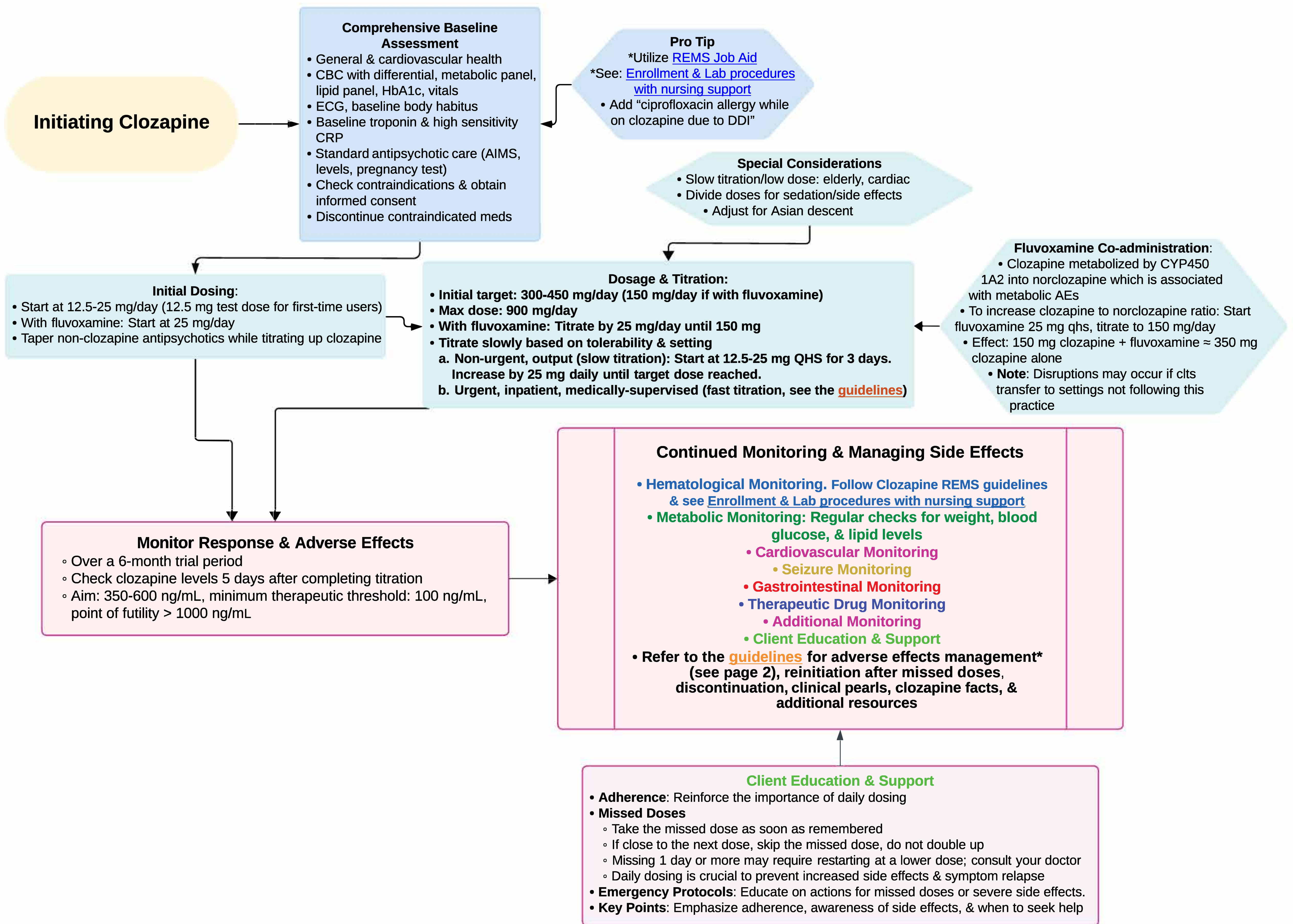
Guidelines for Prescribing & Monitoring Clozapine



Monitoring & Adverse Effects Management*

Hematological

- **Frequency**: Weekly (first 6 months), biweekly (second 6 months), then monthly
- **Manage neutropenia based on ANC thresholds**
  - **Normal**: 1.5 – 8 x $10^3/\mu L$
  - **Mild**: 1 – 1.499 x $10^3/\mu L$ (monitor 3x/week until ANC > 1.5 x $10^3/\mu L$)
  - **Moderate**: 0.5 – 0.999 x $10^3/\mu L$ (interrupt clozapine, daily monitoring until ANC ≥ 1 x $10^3/\mu L$, then may resume)
  - **Severe**: < 0.5 x $10^3/\mu L$ (discontinue & increase ANC monitoring, can resume when ANC > 1.5 x $10^3/\mu L$ if benefits outweigh risks)
  - **Confirmatory test** within 24 hours if ANC < 1.5 x $10^3/\mu L$
- **Managing Agranulocytosis**: Consider filgrastim for expedited ANC recovery (impact on infection rates/mortality is unclear)
- **Note**: A significant portion of African Americans have **Benign Ethnic Neutropenia**, leading to lower ANC levels but not necessarily higher risk of severe neutropenia
- **ANC Calculation**: ANC = WBC count × (percentage of segs + percentage of bands) / 100. WBC count is in cells/μL; segs & bands are percentages

Metabolic

- Weight, waist circumference, BP, fasting glucose or HbA1c, lipid panel at regular intervals
- Address abnormalities through lifestyle modifications & pharmacological interventions (e.g. metformin, topiramate, GLP-1 receptor agonists, or fluvoxamine co-administration). Clozapine has lower metabolic risks compared to olanzapine

Cardiovascular

- **Myocarditis**: Monitor particularly during first 4-8 weeks; assess symptoms & vitals at each visit
  - Weekly troponin I & high sensitivity CRP for 8 weeks; troponin T if I unavailable
  - CRP > 100 mg/L & troponin > 2x normal limit are critical indicators in symptomatic pts. Eosinophil Count may rise, but less reliable.
  - **Echocardiography:** If myocarditis/cardiomyopathy is suspected.
- **ECG**: Baseline, annual; QTc risk. Assess ventricular & valve function if myocarditis/cardiomyopathy suspected
- Monitor for orthostatic hypotension, bradycardia, syncope

Seizure

- **Inquire** about seizure history, monitor for myoclonic jerking
- **If Seizure Occurs**: Hold clozapine for 24 hours, reduce dose by 50%, consider adding anticonvulsant
- **Reder to the Guidelines for Anticonvulsant Options**. Clozapine titration can be resumed after an anticonvulsant is added
- **Note**: 10% risk of generalized tonic-clonic seizures after 4 years; risk increases with dose (*doubling at 300-600 mg/day and tripling at > 600 mg/day)*

Gastrointestinal

1. **Constipation**
   - **Prevalence**: 32-60% with clozapine
   - **Monitoring & Prophylactic Treatment**
     - **Diet & Lifestyle**: High-fiber foods, adequate fluids, exercise
     - **Stool Softeners**: DSS 250 mg or Miralax 17g at initiation
     - **Laxatives**: Dulcolax 10 mg or Senna 17.2 mg daily
     - **For Constipation**: PRN lactulose; consider lubiprostone or linaclotide for non-responsive cases
   - **Note**: Risk of paralytic ileus with fatality rate of 15-28% if untreated (vs *severe neutropenia fatality rate: 2 – 4%)*
2. **Hypersalivation**
   - **Prevalence**: 90% with greater severity at night
   - **Management**: Reder to the Guidelines

Therapeutic Drug Monitoring

- **Check Levels**: During titration, poor response, or suspected non-adherence; draw in AM, 8-10 hours after the PM dose. Initial monitoring is essential due to metabolic variability; ongoing monitoring though not mandated, aids adherence
- **Target Range**: 350-600 ng/mL; adjust based on response & side effects
- Monitor response for 2 weeks after reaching therapeutic level before further dosage ncrease
  - Consider > 350 ng/mL for refractory symptoms; evidence of efficacy is limited

Additional Monitoring

- Smoking, caffeine intake, NMS, hepatotoxicity, PE, anticholinergic toxicity, cognitive/motor performance