Pharmacological Treatment of Schizophrenia: Current Evidence Base

Outline

- Introduction
- History
- General Principles
- Management algorithms
- Routes of administration and dosing
- Landmark studies
- Classification of antipsychotics
- Adverse Effects
- Summary

Introduction

- Antipsychotics – reduce psychotic symptoms; even eliminated
- Minimize recurrence
- -ve symptoms & cognitive dysfunction – inadequately treated
- Antipsychotics may worsen SCZ associated health problems

History

- Late 19th & early 20th century – prolonged hospitalization; somatic treatment, bromides & barbiturates, hydrotherapy & wet sheet packs
- Early 1920s – Barbiturate sleep treatment
- 1930s – Insulin coma treatment
- 1935 – Prefrontal lobotomy (Moniz)
- Convulsive therapies – drugs (camphor, pentylenetetrazol), ECT

History

- Early 1950s – Reserpine, Chlorpromazine (Laborit), Thioridazine, Fluphenazine
- 1960s – Clozapine, introduced in 1990s
- 1994 – Risperidone
- 1996 – Olanzapine
- 1997 – Quetiapine

- Insulin coma treatment was introduced during the 1930s. Patients were
- administered gradually increasing doses of insulin until a coma was
- introduced. After an hour of monitoring, glucose was administered,
- terminating the coma. Patients were commonly administered as many as
- 20 comas. Insulin coma was widely used in the treatment of psychosis,
- suggesting that it may have been somewhat effective. Unfortunately, it was
- never exposed to adequate research trials, and it remains unclear if the
- treatment was effective. It was abandoned when antipsychotics were
- introduced.

History

- 2001 – Ziprasidone
- 2002 – Aripiprazole
- 2007 – Paliperidone
- 2009 – Asenapine, Iloperidone
- 2010 – Lurasidone
- 2015 – Brexipiprazole, Cariprazine

General Principles

- Establish therapeutic alliance with pt. and relatives
- Target broad range of symptoms
- Treatment – continuous, intense and uninterrupted
- Target other substance use/abuse
- Target other comorbid conditions
- Minimize initial discomfort
- Family involvement

Advantages of SGAs over FGAs

SGAs – 1st line management of schizophrenia

- Target –ve symptoms
- Mild improvement in cognitive impairment
- Less A/E (EPS and tardive dyskinesia)
- Comparable to FGAs for resolution of +ve symptoms
- Less duration of hospitalization
- Better compliance (well tolerated)

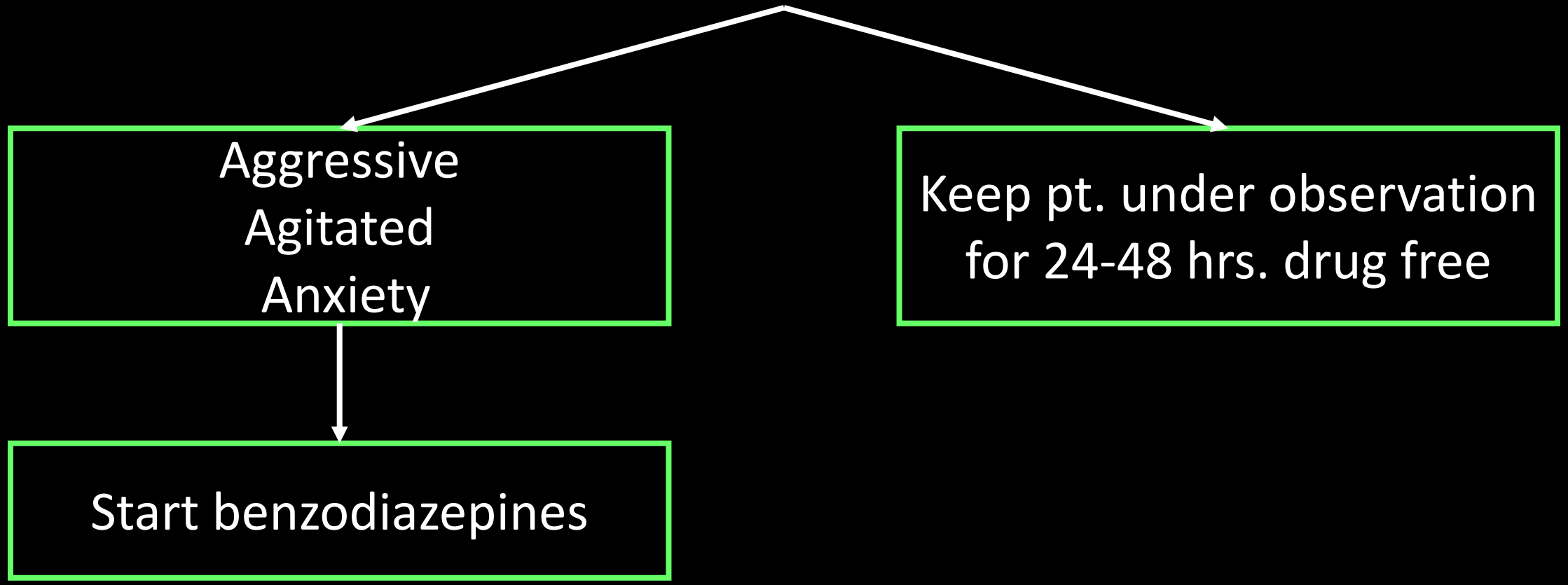
First Episode Schizophrenia

- More R_x responsive ∴ lower antipsychotic doses (~50%)
- More sensitive to A/E
- Low insight ∴ high risk for nonadherence, relapse, psychosocial deterioration & suicidality
- Requires multidisciplinary interventions, focusing on engagement, treatment continuation, relapse prevention, physical health & functional recovery

Indications & Assessment

- Start R_x ASAP – delays worsen long-term course
- Brief delay – diagnostic evaluation & rule out other causes
- Physical, neurological & MSE; lab. I_X
- Assess movement disorders
- Safe to start antipsychotics before lab. I_x (Except clozapine)
- Agitated/aggressive pts. – R_x started before medical evaluation

First Episode Schizophrenia



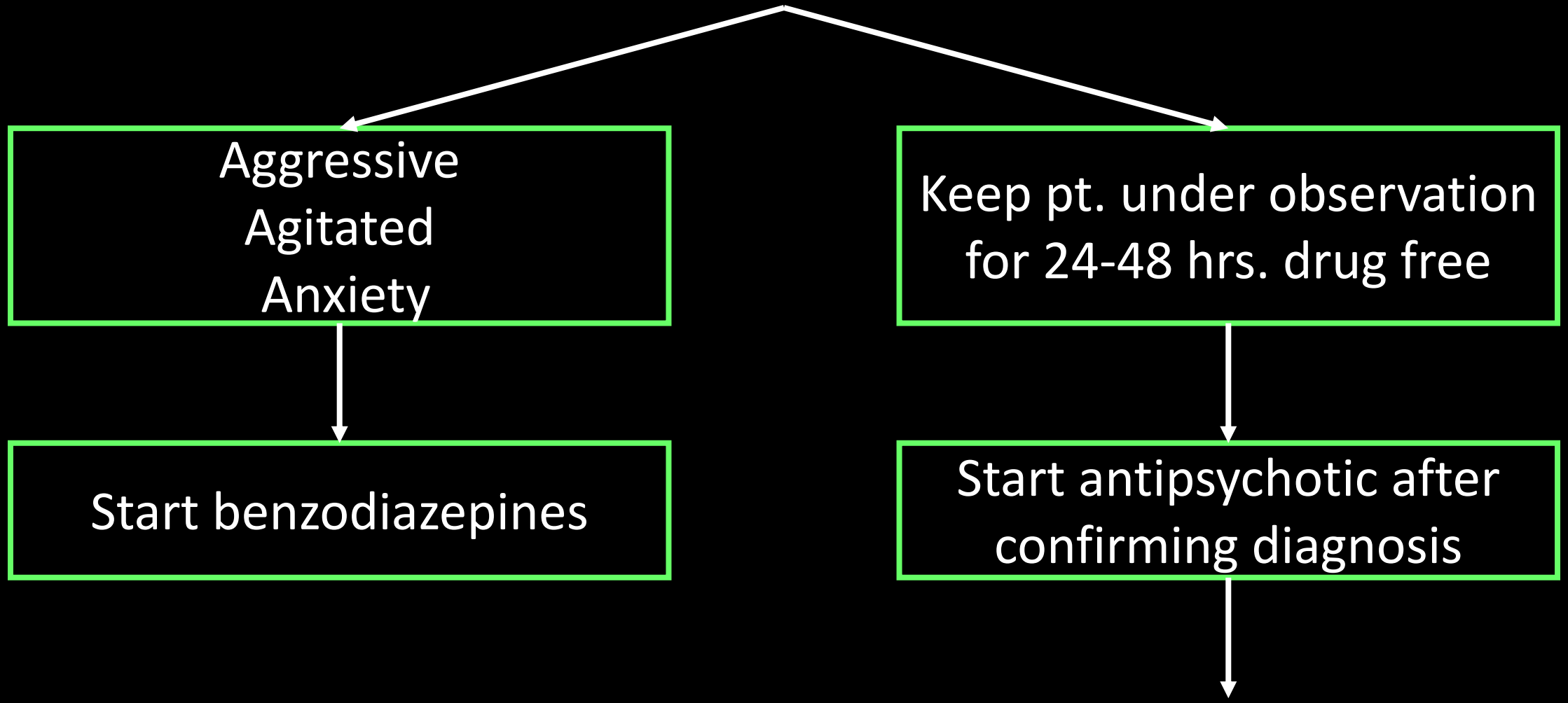
Agitated State

- Agitation d/t delusions/suspiciousness or drug abuse/withdrawal/akathisia
- Akathisia mimics agitation
- ↑ antipsychotic (AP): improves agitation but worsens akathisia
- Benzodiazepine (BZD): improves agitation and akathisia
- ↑ potency AP: calming without excessive sedation

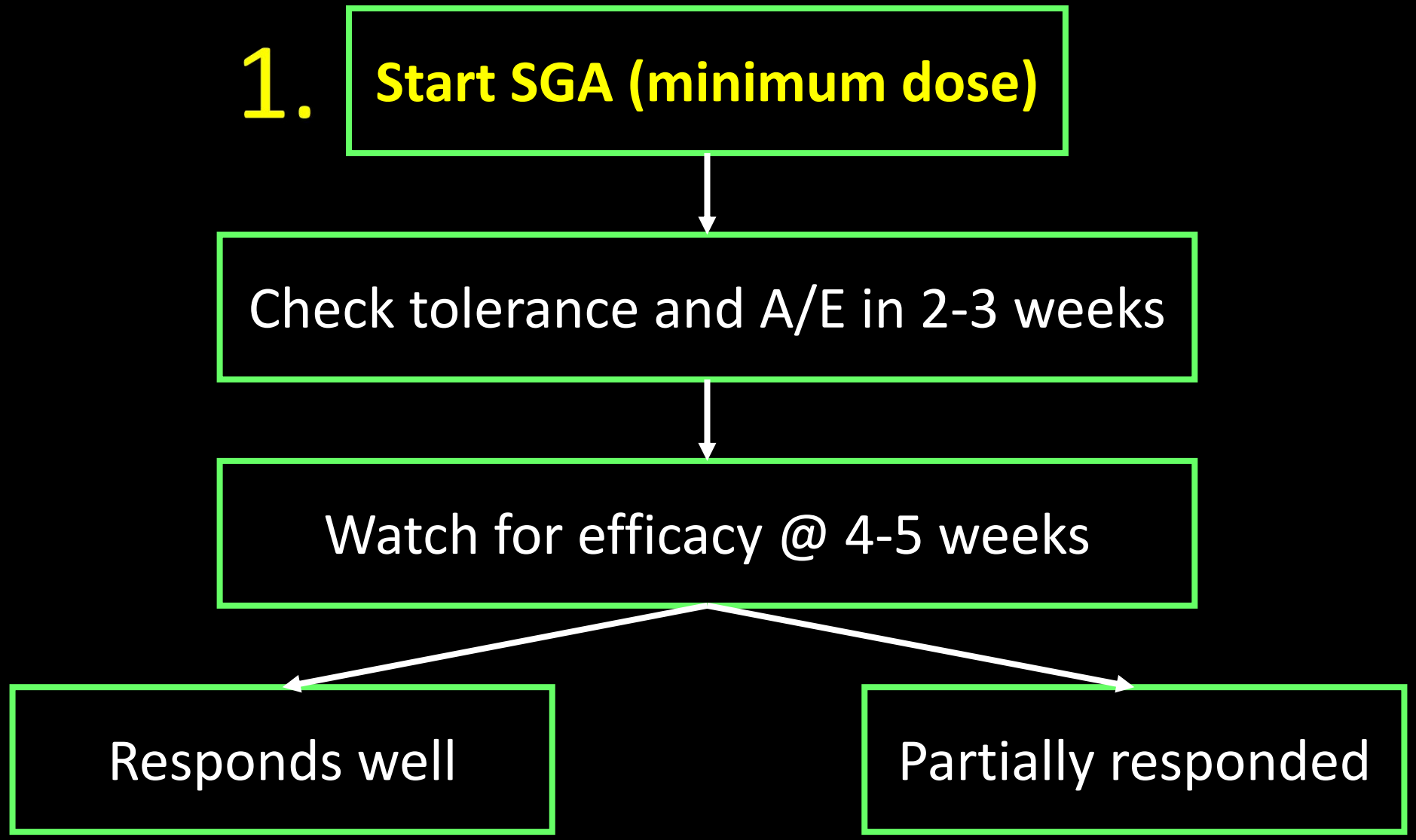
Agitated State

- IM SGAs > FGAs d/t less EPS (dystonia/akathisia)
- FGAs + anticholinergic/antihistaminic → less EPS
- Alternative: rapidly dissolving oral SGAs
- BZD + AP > Higher doses of AP; reduces AP doses

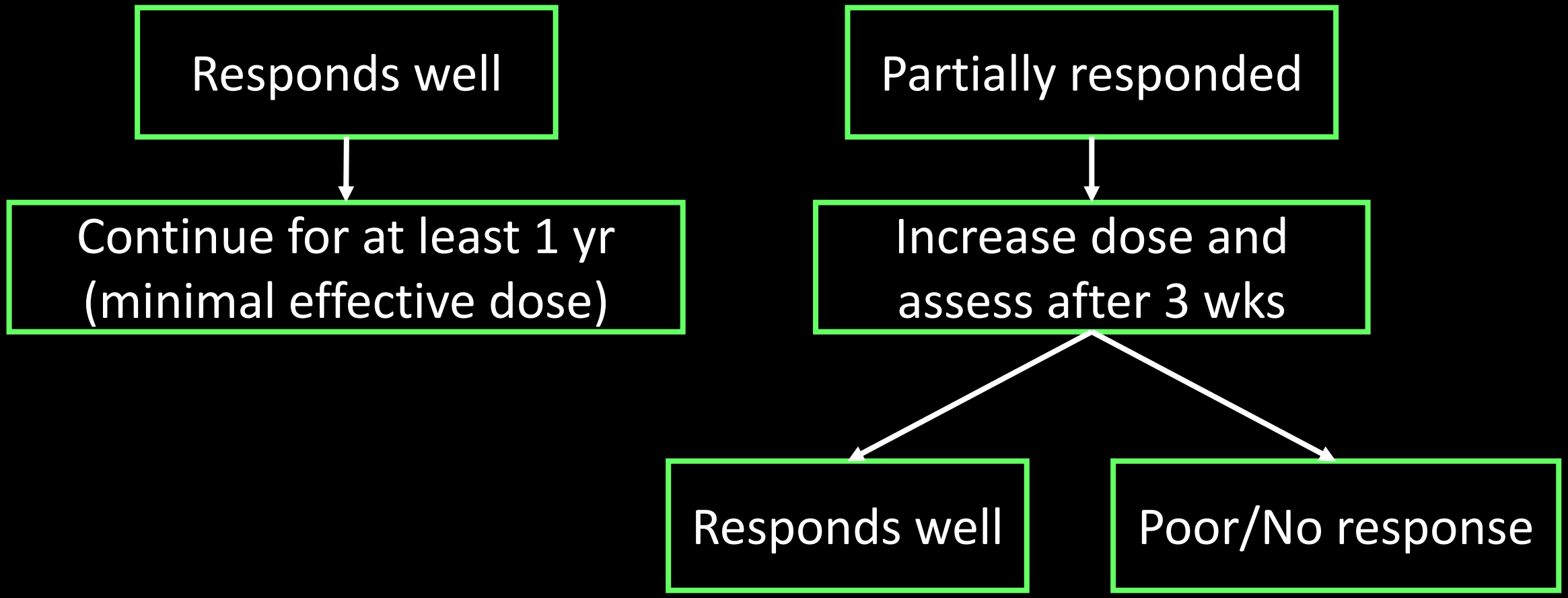
First Episode Schizophrenia



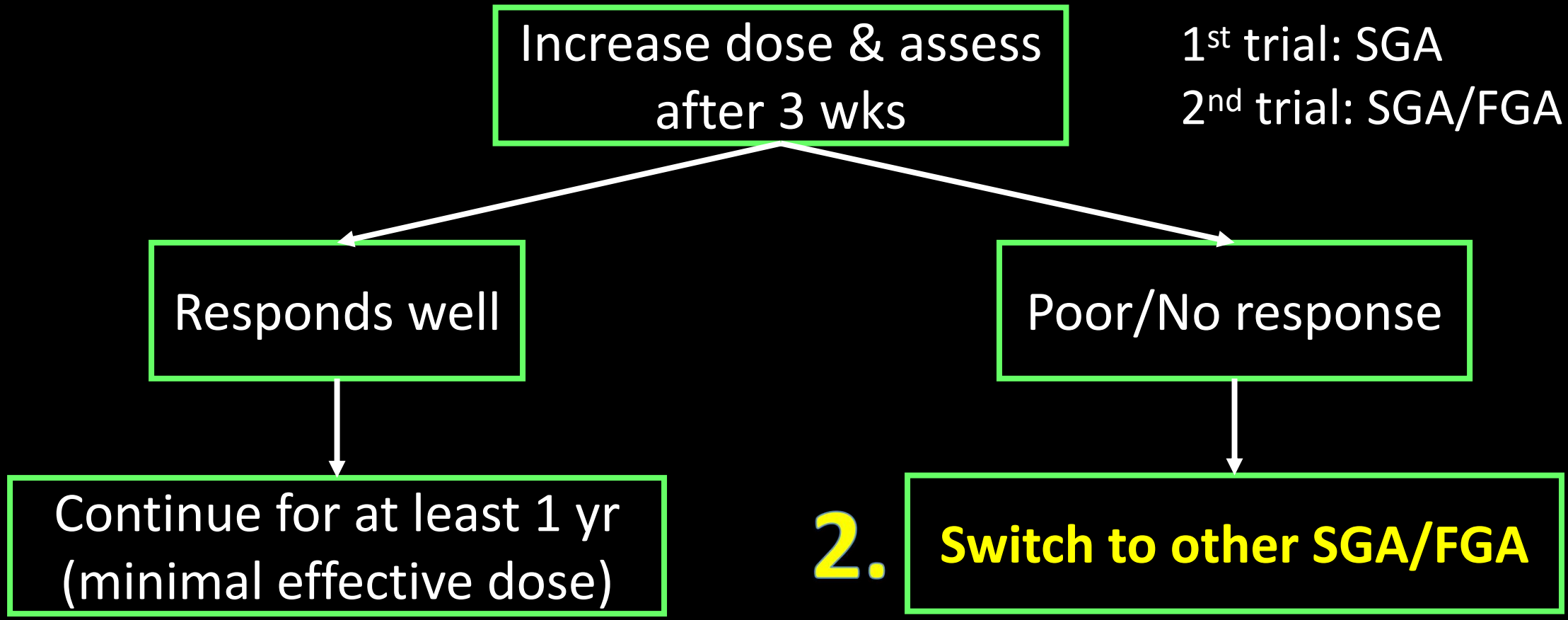
First Episode Schizophrenia



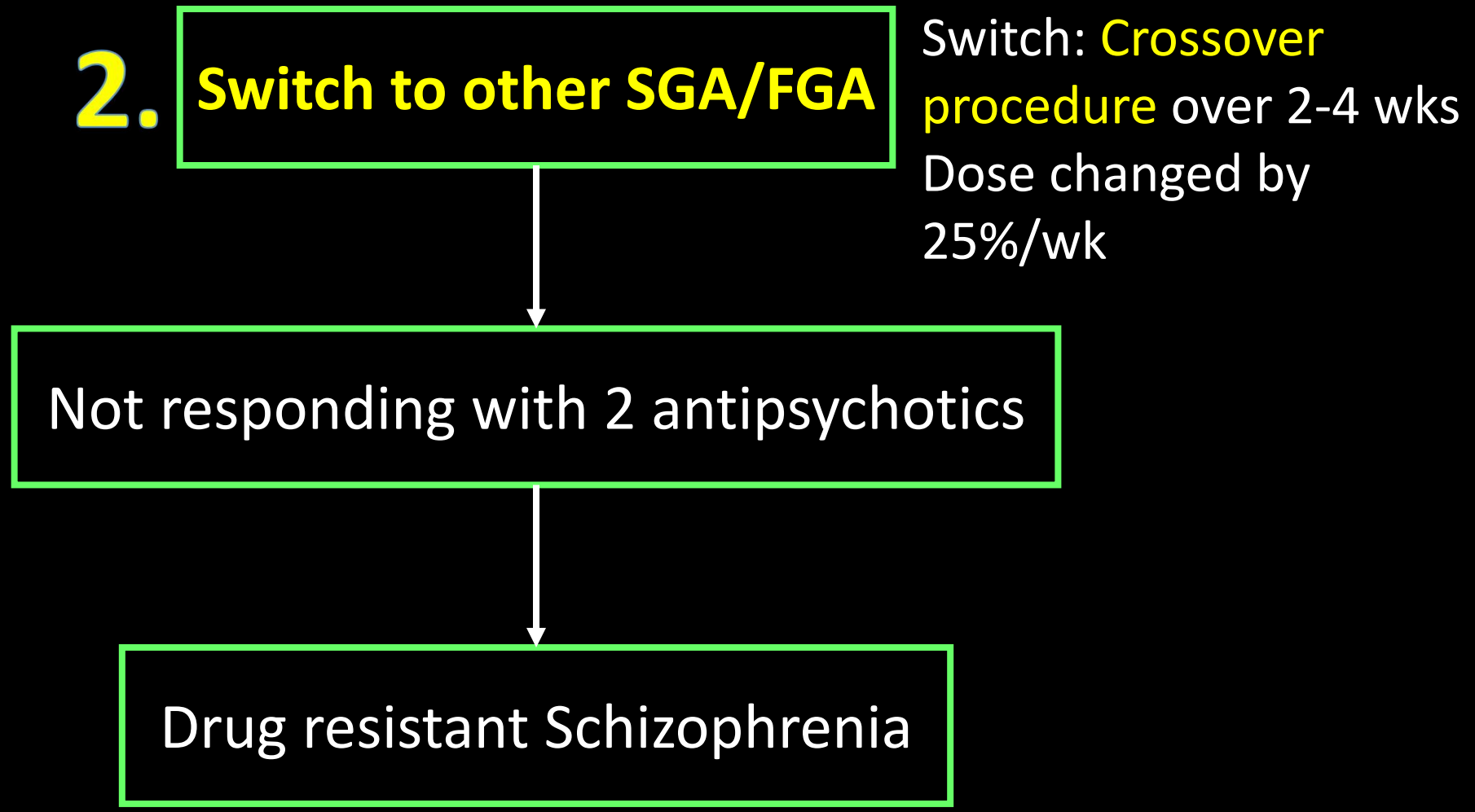
First Episode Schizophrenia



First Episode Schizophrenia



First Episode Schizophrenia



Routes of Administration

- Start orally; Peak plasma levels within 1-6 hours
- Short-acting IM drugs: pt. refuses orally or very rapid onset desired; Peak plasma level within 30 mins.
- Long-acting injectables: continuation/maintenance phase; released slowly over several weeks; Peak plasma levels weeks to months
  - FGA: Haloperidol, Fluphenazine (Oil based)
  - SGA: Olanzapine, Risperidone, Aripiprazole & Paliperidone (Water based)

Dosage Selection

Drug	First Episode (mg)	Multi-episode (mg)
FGAs		
Chlorpromazine	200	300
Haloperidol	2	4
Sulpiride	400	800
Trifluoperazine	10	15
SGAs		
Amisulpiride	400	400
Aripiprazole	10	10

Dosage Selection

Drug	First Episode (mg)	Multi-episode (mg)
SGAs		
Asenapine	10	10
Iloperidone	4	8
Lurasidone	37	37
Olanzapine	5	7.5
Quetiapine	150	300
Risperidone	2	3
Ziprasidone	40	80

Equivalent Doses

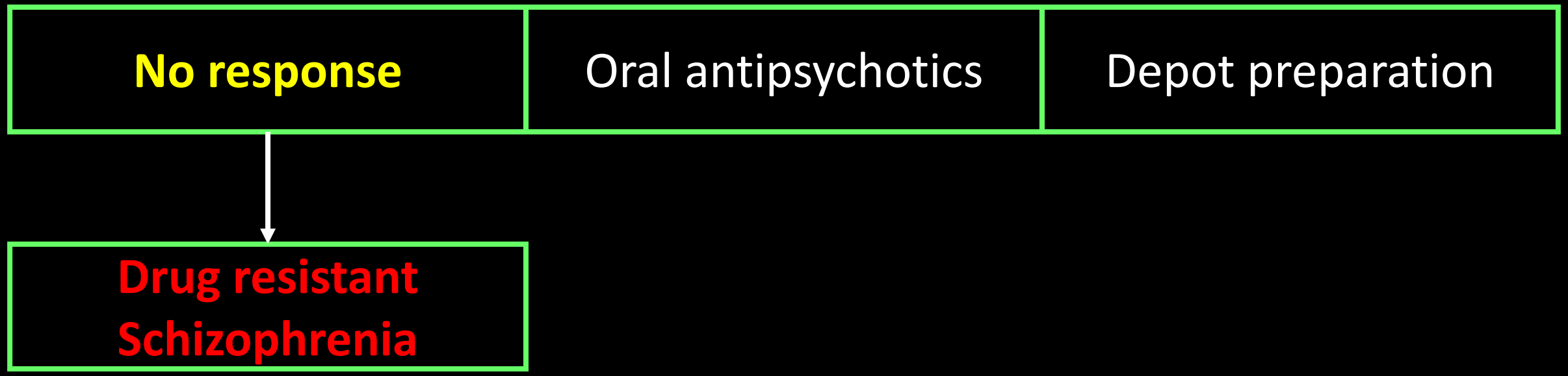
Drug	Equivalent Dose (mg/day)
Chlorpromazine	100
Flupenthixol	3
Fluphenazine	2
Haloperidol	2
Pimozide	2
Sulpiride	200
Trifluoperazine	5
Zuclopenthixol	25

Drug	Equivalent Dose (mg/day)
Aripiprazole	10
Asenapine	10
Iloperidone	8
Lurasidone	37
Olanzapine	7.5-10
Quetiapine	300
Risperidone	3
Ziprasidone	40

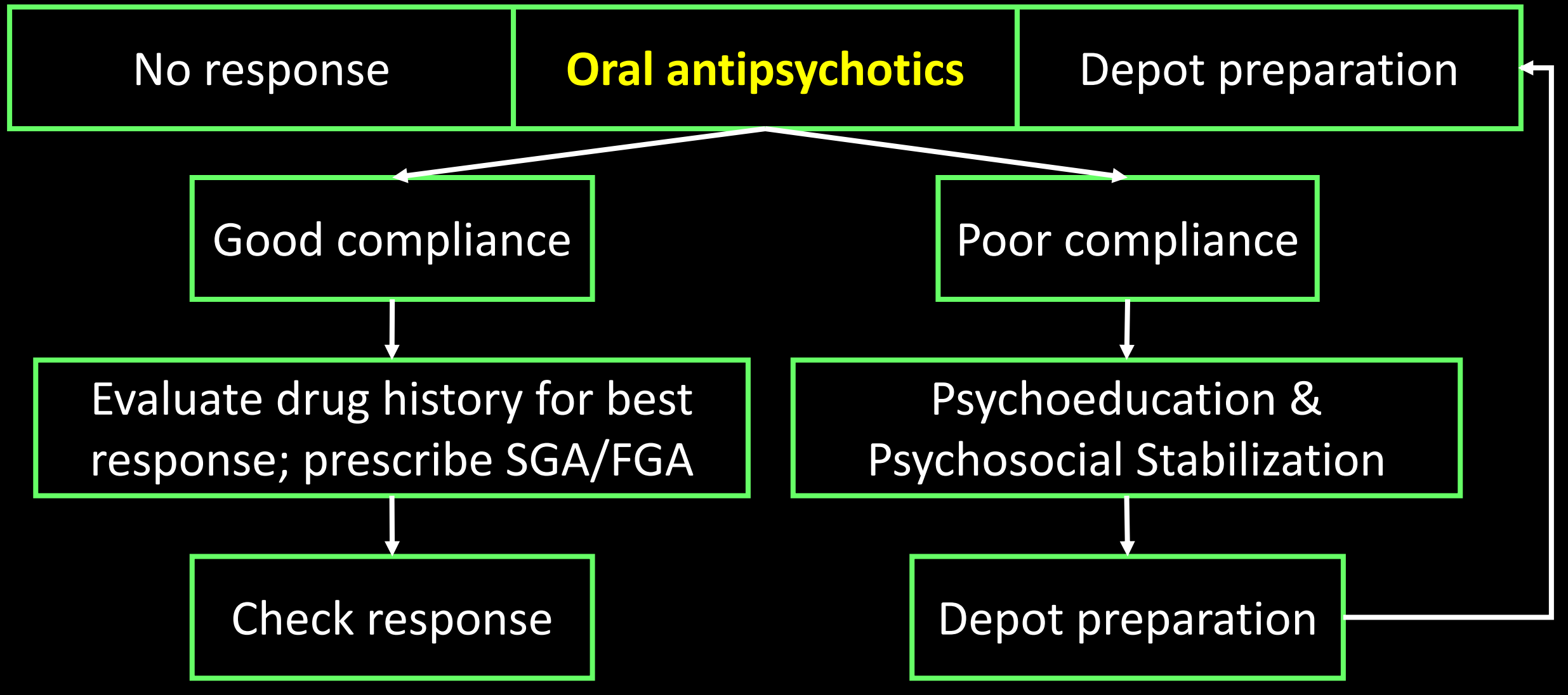
Multiple Episode Psychosis

No response	Oral antipsychotics	Depot preparation

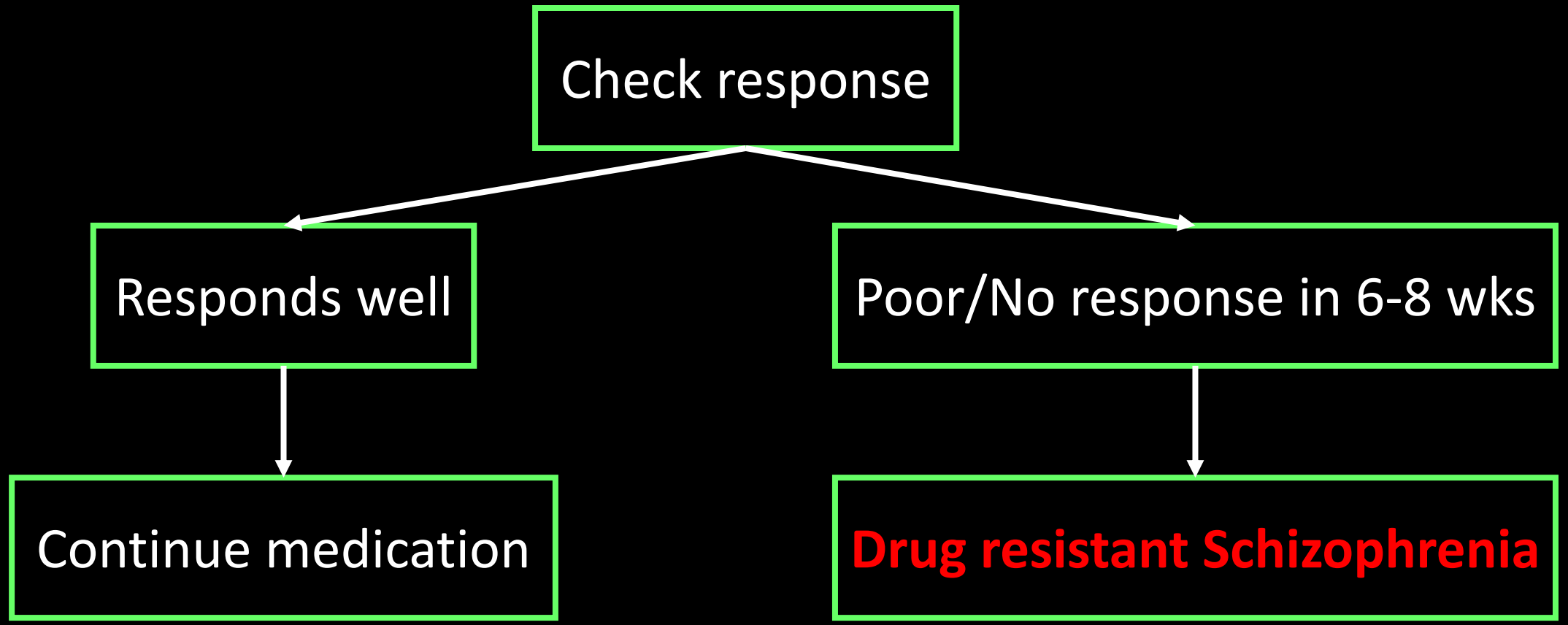
Multiple Episode Psychosis



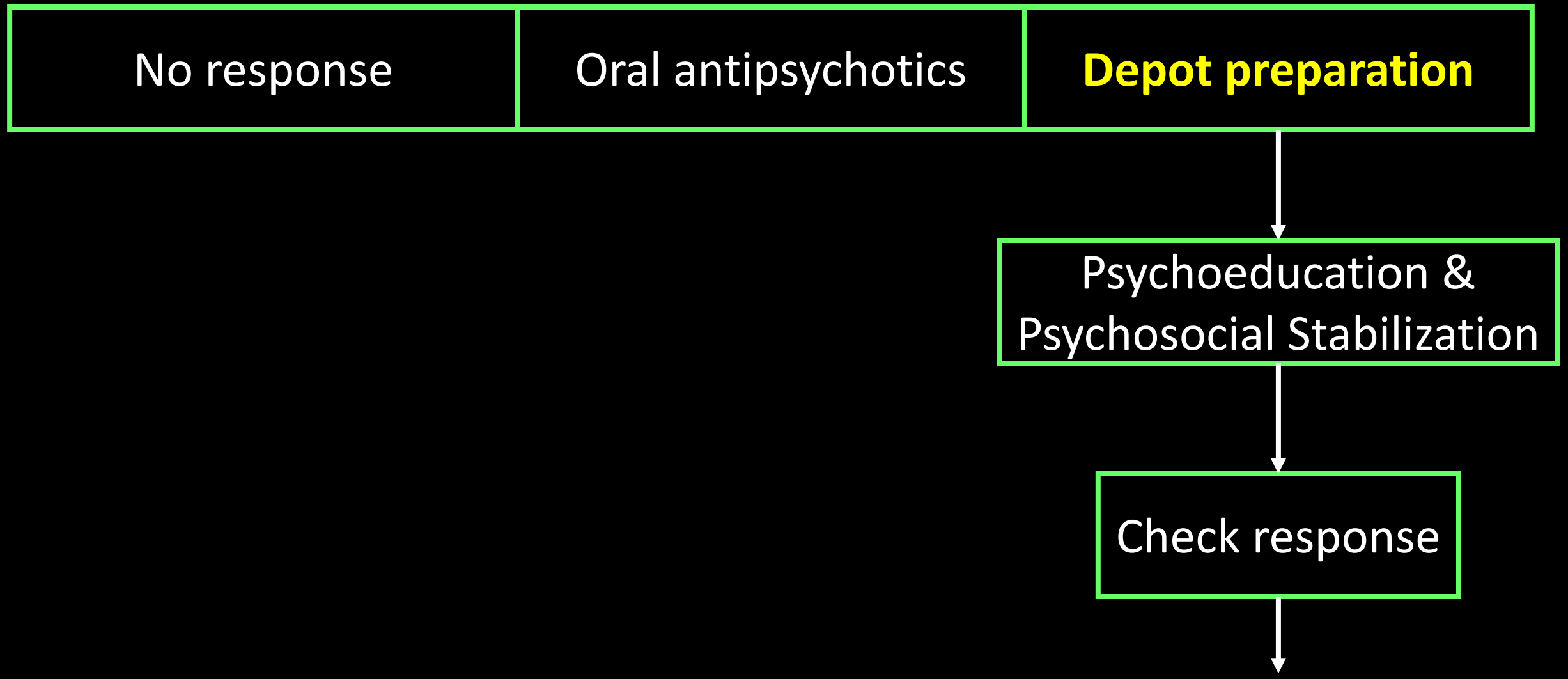
Multiple Episode Psychosis



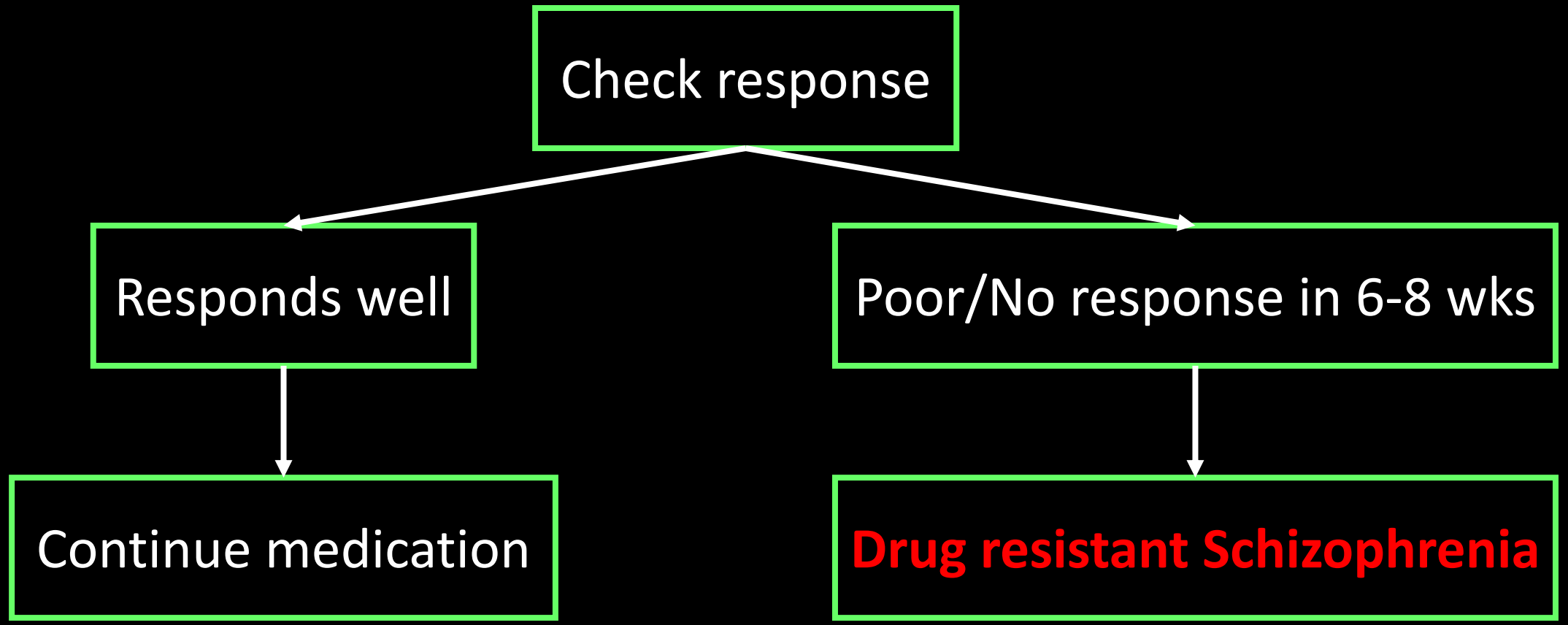
Multiple Episode Psychosis



Multiple Episode Psychosis



Multiple Episode Psychosis



Advantages of Depot Preparation

- Better compliance
- Low fluctuations in serum drug levels (steady state plasma conc.)
- Close follow-ups of patients
- Avoid in drug-naïve pts; first use long acting SGA (Penfluridol)

Advantages of Depot Preparation

- Drugs available:
  - Aripiprazole
  - Flupentixol decanoate
  - Fluphenazine decanoate
  - Haloperidol decanoate
  - Olanzapine pamoate
  - Paliperidone palmitate
  - Risperidone microspheres
  - Zuclopenthixol decanoate

Drug Resistant Schizophrenia

1. Patient exposed to 2 different antipsychotics (one should be a SGA)
2. 6-8 weeks exposure to an antipsychotic with dose equivalent of 200-400mg chlorpromazine
3. Compliance (Check for alternative diagnosis)

- DOC: Clozapine
- ECT

Indications for ECT

1. Suicidal attempt
2. Suicidal ideation
3. Lethal to self
4. Lethal to others
5. Catatonia (2nd line after BZD)
6. Drug resistant schizophrenia
7. Not taking oral medication/resisting treatment

Treatment Duration for Relapse Prevention

- 1st Episode Schizophrenia
  - Duration: 12-24 months
  - Relapse rate: 70-90%
  - 20% - symptom free
- Two or more relapse rate
  - Prolonged Rx upto 5 yrs
  - Abrupt discontinuation a/w 50% higher rate of relapse within 6 months as compared to slow reduction of dose
  - Do not decrease dose by > 20% over 4-8 weeks

Negative, Mood and Cognitive Symptoms

- 2 types:
  - Primary: illness related
  - Secondary: non-illness related factors (depression, suspiciousness, social anxiety, EPS, sedation, sleep apnoea, chronic pain)
- Primary: ↑ SGAs dose ± antidepressants
- Secondary: ↓ dose, changing drug, antidepressant, antiparkinsonian
- Most effective: Amisulpiride; clozapine also showed improvement
- Persistent –ve Sx: NMDA Rs stimulating agents (Glycine)
- Others: D-serine, D-cycloserine

Negative, Mood and Cognitive Symptoms

- Cognitive impairment: d/t depression, thought disorganization or hallucinations, substance abuse, side effects (EPS, sedation & A/E of anticholinergic & antiparkinsonian medication)
- ↓ anticholinergics, change drug (SGA)
- No AP proven to improve cognitive symptoms
- Suicide risk: 20-40%; 5-10% succeed
- Depression & substance abuse ↑ risk
- Clozapine: prevention of suicidal behaviour

Pregnant & Breastfeeding Population

- Placental passage ratio:
  - Olanzapine > Haloperidol > Risperidone > Quetiapine
- Avoid polypharmacy: ↑ teratogenicity
- 2 cohort studies: No evidence of ↑ risk of major malformation in infants exposed to clozapine, olanzapine, risperidone & quetiapine
- May induce maternal hyperglycaemia, impaired glucose tolerance, weight gain & increase in birth weight

Pregnant & Breastfeeding Population

- Olanzapine: ↑ birth weight, 4 cases of NTD; concomitant medication
- Risperidone: Congenital anomalies (no recurrent patterns)
- Injectable risperidone: 1 case reported: normal baby
- Quetiapine: 8 major malformations of unknown typology
- Aripiprazole/Ziprasidone: limited human studies
- SGAs (Olanzapine, clozapine, risperidone): a/w gestational diabetes

Pregnant & Breastfeeding Population

- Haloperidol: do not appear to increase risk of teratogenicity; limb anomalies reported
- Also used for agitation in pregnant women
- 2nd line: BZD, BZD + FGA
- CPZ: nonspecific teratogenic effects (low risk)
- Low potency FGAs: higher risk of teratogenic effects

Management

- Risk-benefit ratio analysis
- Planning pregnancies
- Folate supplementation – prevent NTD
- Discussion with patient and family regarding options

Lactation

- FGA: appear safe
- SGA: to be established, may be safe
- Avoid clozapine: agranulocytosis and somnolence in infants, thus contraindicated

Landmark Studies

- FGAs v/s SGAs

1. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study
2. Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS)
3. European First Episode Schizophrenia Trial (EUFEST)

CATIE Study

- Initiated by the NIMH
- Compared FGAs (perphenazine) & SGAs (olanzapine, quetiapine, risperidone, ziprasidone)
- Olanzapine: Longer time before discontinuation despite metabolic disturbances
- Perphenazine: Similar efficacy, EPS comparable with others
- Risperidone: Best tolerated
- Ziprasidone: a/w weight loss; +ve impact on lipids & RBS

CATIE Study

- All 5 medications: comparable changes in PANSS +ve scores
- Modest improvement in cognition
- Clozapine: Better efficacy
- Olanzapine and Risperidone: Better tolerated

CUtLASS Study

- SCZ pts. requiring change in treatment, SGAs (except clozapine) a/w improved quality of life over 1 year as compared with FGAs
- FGAs: Chlorpromazine, Flupenthixol, Haloperidol, Loxapine, Sulpiride, Trifluoperazine, Zuclopenthixol, Fluphenazine
- SGAs: Risperidone, Olanzapine, Amisulpride, Quetiapine

CUtLASS Study

- No significant differences in therapeutic response to FGAs and SGAs
- No disadvantage across 1 year in terms of quality of life, symptoms, or associated costs of care was seen in using FGAs v/s non-clozapine SGAs
- No clear preference for either drug group; costs were similar

EUFEST Study

- Assess effectiveness of FGA (low dose haloperidol) v/s SGAs (regular doses of Amisulpiride, Olanzapine, Quetiapine & Ziprasidone)
- SGAs: lower risk for discontinuation
- No group differences in PANSS total scores

EUFEST Study

- Quetiapine > Risperidone & Olanzapine:
  - ↓ PANSS total score (P & G)
  - ↓ CGI-S score
  - ↑ GAF-F score
- Drugs: comparable performance in terms of tolerability
- Olanzapine: weight gain
- Risperidone: galactorrhoea

Summary of Studies

- SGAs differ in tolerability, efficacy & pharmacodynamic profiles
- Little evidence of superior therapeutic efficacy of SGAs over FGAs
- SGAs: fewer EPS & tardive dyskinesia; but greater metabolic A/E than FGAs
- Aripiprazole
- Ziprasidone
- Iloperidone
- Lurasidone

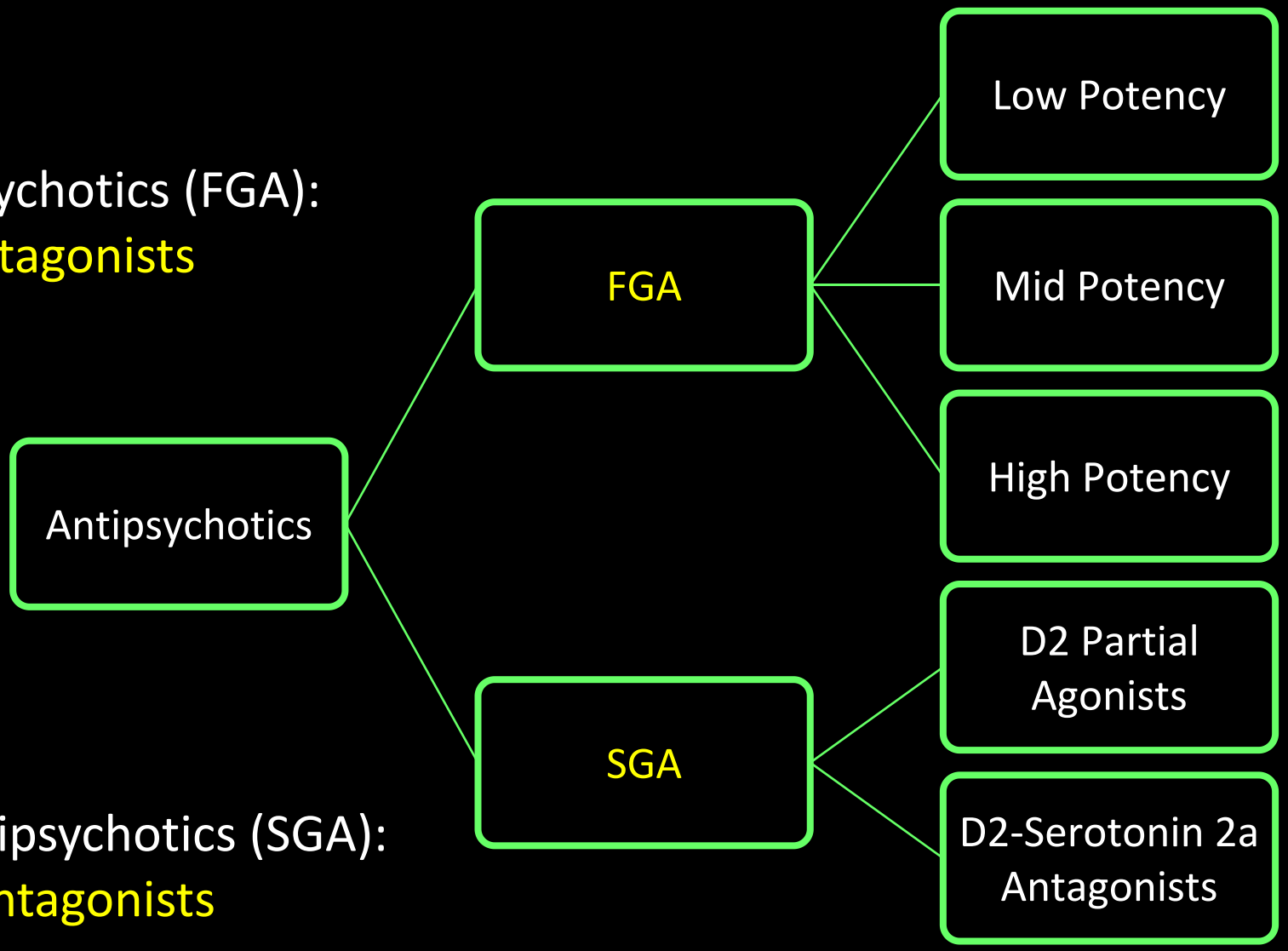
} Least weight & metabolic effects

Summary of Studies

- Risperidone: Acute EPS
- Clozapine & Olanzapine: Hyperglycaemia, dyslipidaemia & weight gain
- Amisulpride & Risperidone: Hyperprolactinaemia
- Ziprasidone: QT prolongation
- Clozapine: Sedation, antimuscarinic symptoms, postural hypotension, agranulocytosis & seizures
- Asenapine: Hypersensitivity

Classification

First Generation Antipsychotics (FGA):
Dopamine Receptor Antagonists



Second Generation Antipsychotics (SGA):
Serotonin-Dopamine Antagonists

First Generation Antipsychotics (FGA)

Chemical Class	Side Chain	Potency	Drug
Phenothiazines	Aliphatic	Low/Medium	Chlorpromazine Trifluprомazine
	Piperidine	Low/Medium	Thioridazine
	Piperazine	Medium/High	Perphenazine Fluphenazine Trifluoperazine
Butyrophenones		High	Haloperidol Trifluperidol Penfluperidol
Thioxanthenes		Low/Medium	Flupenthixol Zuclopenthixol Thiothixene
Dibenzepines		Low/Medium	Loxapine
Diphenylbutylpiperidines		High	Pimozide

Second Generation Antipsychotics (SGA)

Partial D2 Agonists
• Aripiprazole • Amisulpiride • Brexipiprazole • Cariprazine

Dopamine D2- Serotonin 2A Antagonists
• Asenapine • Amisulpiride • Clozapine • Iloperidone • Lurasidone • Olanzapine • Paliperidone • Quetiapine • Risperidone • Ziprasidone

Adverse Effects

Adverse effect	Antipsychotic associated
EPS	High potency FGAs, risperidone, high dose olanzapine
Anticholinergic effects	Thioridazine, chlorpromazine, clozapine
Weight gain	FGAs, clozapine, olanzapine, high dose risperidone & quetiapine
Hyperprolactinemia	FGAs, risperidone
CVD	Risperidone, olanzapine, aripiprazole
Sedation	FGAs, clozapine, olanzapine, quetiapine, aripiprazole
Orthostatic hypotension	Low potency FGAs, clozapine, quetiapine
Increased mortality in elderly pts. with dementia	SGAs

Risk Factors for EPS

- Children/adolescent
- Males (except parkinsonism/tardive dyskinesia)
- Initial high dose
- Rapid increase in dose
- Reduction in initial high doses
- Previous history of EPS

EPS	Acute Dystonia	Pseudo-parkinsonism	Akathisia	Tardive Dyskinesia
Prevalence	10%; more common • In young males • In drug naïve • With high potency AP Rare in elderly	20%; more common in: • elderly females • those with pre-existing neurological damage	25%; less with SGAs; most with aripiprazole, least with clozapine	5%; more common in: • elderly women • those with affective illness • those who have had acute EPS early in treatment
Signs & Symptoms	Muscle spasm • Oculogyric crisis • Torticollis • Unable to swallow/speak • Opisthotonus • Jaw dislocation	• Tremor/rigidity • Bradykinesia • Slow thinking • Salivation	Inner restlessness • Foot stamping • (un)crossing legs • Pacing up & down	• Lip smacking/chewing • Tongue protrusion • Choreiform hand movements • Pelvic thrusting
Time taken to develop	Mins. to hours	Days to weeks	Hours to weeks	Months to years
Prevention/Treatment	• Anticholinergic • ECT • Change drug • Botulinum toxin • rTMS	• Decrease dose • Change drug • Anticholinergic	• Decrease dose • Change drug • Beta-blocker • Low dose clonazepam • 5HT2 antagonists	• Stop anticholinergic • Decrease dose • Change drug • Clozapine

Tardive Dyskinesia

Diagnostic Criteria

- Continuous antipsychotic treatment for a period of at least 3 months
- Abnormal involuntary movements
  - Moderately prominent in 1/more body regions **OR**
  - Lightly prominent in >2 body regions
- Rule out other causes for involuntary hyperkinetic dyskinesias
- Onset within 1 month of discontinuation of treatment

Anticholinergic A/E

Central	Peripheral
• Confusion • Disorientation • Agitation • Delirium	• Constipation • Urinary retention • Glaucoma • Dry mouth

Hyperprolactinemia

- Dopamine (DA) inhibits PRL release, ∴ DA antagonists ↑ prolactin (PRL) levels
- Dose related; seen with FGAs, risperidone, paliperidone
- No increase in PRL: clozapine, olanzapine, quetiapine, lurasidone, ziprasidone
- ↓ PRL: Partial D2 agonist (Aripiprazole, Brexiprazole, Cariprazine)
- Sexual dysfunction, ↓ bone mineral density, menstrual disturbances, gynaecomastia & galactorrhoea

Management of Hyperprolactinemia

- ↓ dose
- Switch to non-PRL elevating drug
- Add and continue aripiprazole; gradually withdraw offending drug
- Hormone replacement therapy (estrogen/progestogen for women; testosterone in men)
- Offending drug cannot be changed, dopamine agonists (amantadine, cabergoline and bromocriptine) may be used, but can worsen psychosis

Weight Gain

- Antipsychotics: weight-inducing agents
- Mechanism: 5HT 2C antagonism, H1 antagonism, hyperprolactinaemia & increased serum leptin
- No evidence of direct metabolic effect
- Weight gain d/t increased food intake and reduced energy expenditure
- Waist circumference: > 35” (males) and > 40” (females) – high risk

Weight Gain

High risk	Moderate risk	Low risk
• Clozapine • Olanzapine	• Chlorpromazine • Iloperidone • Quetiapine • Risperidone • Paliperidone	• Amisulpride • Asenapine • Aripiprazole • Haloperidol • Lurasidone • Sulpiride • Trifluoperazine • Ziprasidone

Management of Weight Gain

- Switch to aripiprazole, ziprasidone or lurasidone
- Calorie restriction, low glycaemic index diet, diet/exercise programmes
- Drugs: Amantidine, Buproprion, Fluoxetine, Metformin, Melatonin, Orlistat, Reboxetine, Topiramate, Zonisamide

Dyslipidaemia

- FGA:
  - Phenothiazines: ↑ TGs & LDL; ↓ HDL
  - Haloperidol: minimal effect
- SGA:
  - ↑ cholesterol & TGs
  - Olanzapine > quetiapine & risperidone > aripiprazole,lurasidone & ziprasidone
  - Clozapine: ↑ TGs (x2), ↑ cholesterol

Dyslipidaemia

Treatment

- Switch drug: Aripiprazole/Ziprasidone
- Clozapine-induced ↑ TG: switch to risperidone
- Dietary advice, lifestyle changes,
- Statins, fibrates (>10% risk of CVD)

Diabetes

Risk	Drugs
High	Clozapine, Olanzapine
Moderate	Quetiapine, risperidone, phenothiazines
Low	High potency FGAs
Minimal	Aripiprazole, amisulpiride, lurasidone, ziprasidone

- Treatment: Switch drug: Aripiprazole/Ziprasidone
- Anti-diabetic drugs (Pioglitazone – hepatotoxic)

Monitoring Protocol

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	x					x	
Weight (BMI)	x	x	x	x	x		
Waist circumference	x			x		x	
Blood pressure	x			x		x	
Fasting plasma glucose	x			x		x	
Fasting lipid profile	x			x			x

Cardiovascular Adverse Effects

- Most common ECG abnormality: QTc prolongation
- Normal: <420ms
- Pathological repolarization: >500ms
- Higher risk of ventricular arrhythmia & *torsades de pointes*
- Risk factors: Hypokalemia, hypomagnesaemia, cardiac disorders, bradycardia, females and older age

Cardiovascular Adverse Effects

Effects	Drugs
No effects	Amisulpiride, Aripiprazole
Low effects	Clozapine, Flupenthixol, Fluphenazine, Haloperidol, Olanzapine, Risperidone, Sulpiride
Moderate effects	Chlorpromazine, Quetiapine, Ziprasidone
High effects	IV antipsychotics, Thioridazine, Pimozide, Sertindole

Hyponatremia

Cause	Drugs implicated	Treatment
Water intoxication (serum and urine osmolality low)	Anticholinergic A/E of APs	• Fluid restriction • Clozapine • No effect of lowering dose • Do not use demeclocycline
SIADH (serum osmolality low; urine osmolality relatively high)	All antipsychotic drugs	• Fluid restriction • Switch drug • Demeclocycline • Lithium
Pseudohyponatremia	Severe hyperlipidaemia and/or hyperglycaemia → secondary increase in plasma volume	• Switch drug

Features: confusion, nausea, headache, lethargy, seizures & coma

Neuroleptic Malignant Syndrome

- Rare (<1%), potentially serious or even fatal
- Dopaminergic antagonism - muscular rigidity & sympathetic hyperactivity
- Clinical features: Fever, diaphoresis, rigidity, confusion, fluctuating consciousness, fluctuating blood pressure, tachycardia
- Investigations: ↑ creatine kinase, leukocytosis, altered LFT

Neuroleptic Malignant Syndrome

Treatment:

- Withdraw antipsychotics
- Monitor temperature, PR, BP – symptomatic Rx
- BZD (Lorazepam)
- Rehydration, bromocriptine + dantrolene, BZD, artificial ventilation if required
- Others: L-dopa, apomorphine & carbamazepine
- Psychosis - ECT

Management of Other Adverse Effects

- Sedation: Low potency FGAs (Chlorpromazine, Thioridazine), SGAs (Clozapine, Olanzapine, Quetiapine)
- Postural Hypotension: Low Potency FGAs, SGAs (Clozapine, Iloperidone
- Tolerance develops over time

Summary

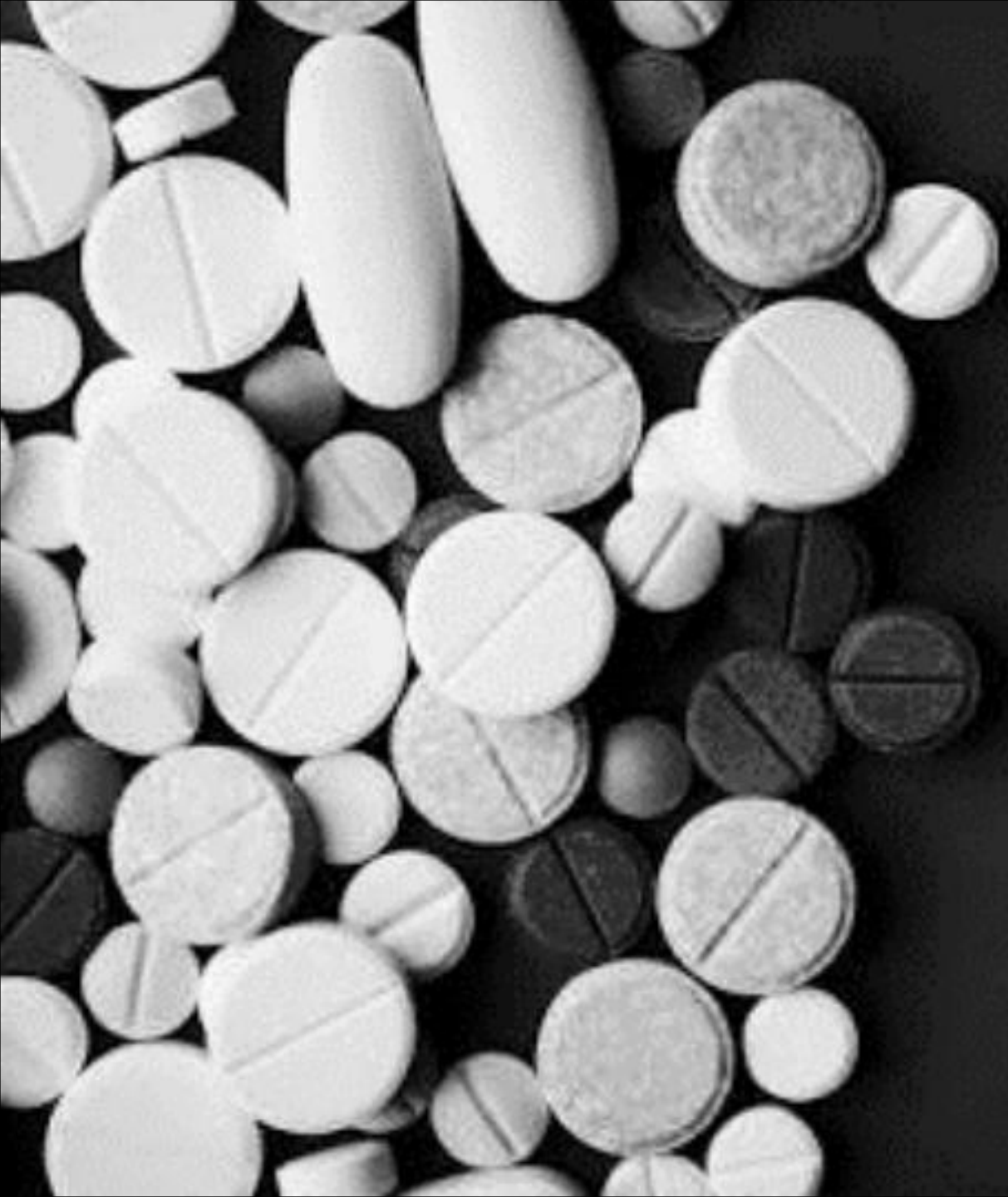
- Establish therapeutic alliance & target broad range of symptoms
- Start R_x ASAP – delays worsen long-term course
- SGAs: fewer A/E than FGAs ∴ 1st line of treatment
- Clozapine: Better response, but not 1st line d/t A/E
- Oral route preferred; injectables for non-compliance

Summary

- BZD: improve agitation & akathisia
- Pregnancy & lactation: Olanzapine & Haloperidol
- Landmark studies: SGAs ≈ FGAs in terms of tolerability/acceptability;
- Olanzapine – good compliance; clozapine – refractory symptoms
- Monitor and prompt treatment of A/E

References

- Benjamin J. Sadock, Virginia A. Sadock, Pedro Ruiz-Kaplan and Sadock's Comprehensive Textbook Of Psychiatry 10th Edition
- The Maudsley Prescribing Guidelines in Psychiatry-12th edition
- The American Psychiatric Publishing - Textbook of Schizophrenia
- K.D. Tripathi - Essentials of Medical Pharmacology, 6th ed
- Stahl's Essential Psychopharmacology 4th Ed
- Babu GN, Desai G, Chandra PS. Antipsychotics in pregnancy and lactation. Indian journal of psychiatry. 2015 Jul;57(Suppl 2):S303



Thank You