PSYCHO-ONCOLOGY GUIDELINES

By : Mohamed Makhlouf

Mental Health MSc,RPh

Basic points:

- Psycho-oncology patients
- Neuropsychiatry complications of Cancer and chemotherapy
- Psychoactive Medications use in paediatric
- Prescribing Tips
- Pharmacokinetics in Children
- Depression Disorder
- Mood Disorders in Children
- Post traumatic stress disorders (PTSD)
- Anxiety and Insomnia Disorders Treatment
- Obsessive Compulsive Disorder
- ADHD Medications
- Pediatric Bipolar Disorder
- Oppositional & Behavioral Disorder
- Autism Spectrum Pharmacotherapy
- Tics and Tourette's syndrome

Psycho-oncology

- Children with Cancer treatment may be overwhelming for patients and their families
- Psychiatric sequel may be from diagnosis or treatment medications may be

chronic like depressed mood, anxiety, Post traumatic stress disorder, behavioural changes, alexithymia ,,

Or acute mental status changes like agitation or aggression, delirium, psychosis and mania

The **rate of depression in cancer patients** is thought to be ≥3 higher than general population

- Cancer patients whom diagnosed with depression have higher **risk of mortality** compared with non-depressed cancer patients
- Somatic symptoms and high pain score are so prevalent with depression
- Some children develop Insomnia, anxiety with nausea or vomiting before going to the hospital
- Quality of life and managing psychiatric comorbidities for cancer patient is a big issue not just a cure

Neuropsychiatry Complications Of Cancer And Chemotherapy

- Frontal lobe tumors produce mental status and personality changes, dementia in 70% of cases.
- Right-frontal tumors tend to display more euphoria, whereas left-frontal tumor display more depression.
- Temporal lobe tumours are similar to those of frontal lobe tumours such as depressed mood with apathy
- parietal lobe tumors may present with alack of awareness of their symptoms/neglect syndromes
- Meningioma patients presented with had higher levels of anxiety and depression
- Tumours of the corpus callosum associated with behavioural symptoms, personality changes, psychosis.
- Thalamic tumours prone to have (memory loss, confusion, and emotional liability)
- Hypothalamic & pituitary gland showed little response to the treatment for depression and these tumours have been associated with eating disorders and hypersomnia
- Cerebellar and brain stem tumours associated with affective disorders, delusions and personality change
- Left hemisphere tumour reported higher levels of emotional disturbance than any other group
- All who are treated with cranial radiation show similar difficulties with cognitive function and attention

Neurocognitive Sequel depend on brain tumour location

Part of the brain	Symptoms
Frontal lobe	• changes in behavior, personality and social skills • depression or mood swings •difficulty with organizing and walking • speech problems
Parietal lobe	•problems with reading or writing •loss of feeling in part of the body •difficulty locating objects (spatial awareness)
Temporal lobe	•trouble learning and remembering new information •forgetting events and conversations •difficulty understanding what is said to you •seizures with strange feelings, smells or deja vu
Occipital lobe	•loss of all or some vision
Cerebellum	•coordination and balance problems •uncontrolled eye movement •stiff neck •difficulty speaking (staccato speech
Brain stem	• coordination problems • double vision • facial weakness and numbness

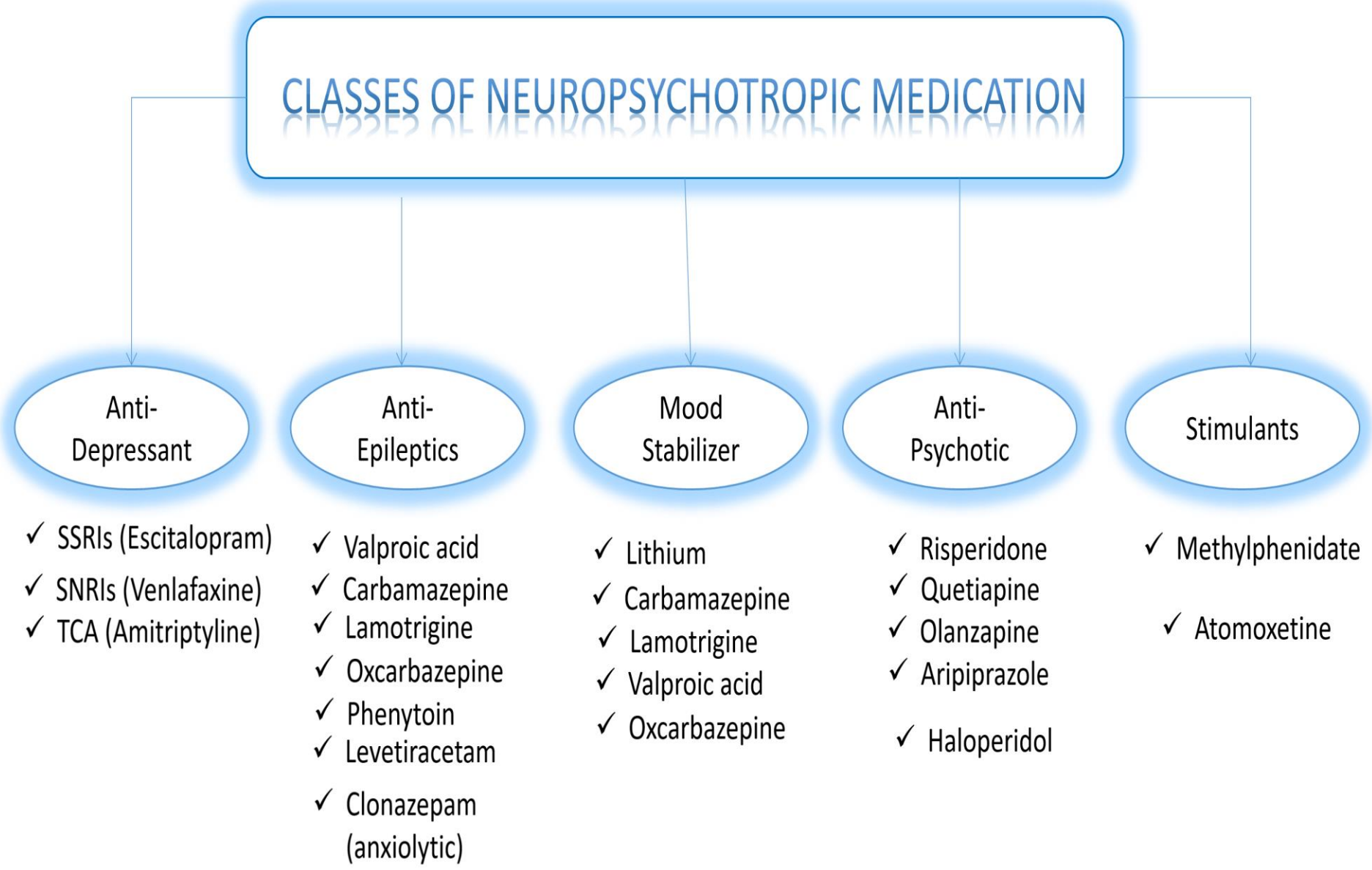
CHEMOTHERAPY INDUCE PSYCHITRIC SYMPTOMS

Medications	Side Effects	Comments
Methotrexate	High risk of seizures	In case of toxicity
Corticosteroids(prednisolone, dexamethasone, etc.)	Psychosis, delirium, mania, depression	1-3% incidence may be dose-related; can also occur on withdrawal
Opioids	Nightmares, anxiety, agitation, depression, psychosis hallucinations, dementia	Usually with high doses
Asparaginase	Confusion, depression, hepatic encephalopathy	
Cytarabine	Confusion	Especially with high doses
Ganciclovir	Psychosis, delirium, confusion	Several reports
Ifosfamide	Encephalopathy, hallucination, confusion, psychosis	Several reports especially in elderly
Valganciclovir	Depression, psychosis, hallucination, confusion, agitation	
Vinblastine , Vincristine	Depression, anxiety hallucinations, depression	May occur commonly and dose-related
Voriconazole	Hallucinations	In case of toxicity

Psychoactive Medications Guidelines in Paediatric

- The UK National Institute for Health and Care Excellence (NICE) guidelines and American Academy of Child and Adolescent Psychiatry (AACAP), The British Association for Psychopharmacology(BAP) recommend that psychological intervention be considered as first-line treatment for depression in children & adolescents then psychopharmacology (fewer evidence-based studies in children than adult psychiatry)
- Pharmacotherapy plus psychotherapy have better results than pharmacotherapy alone
- Psychiatry diagnosis difficulty is very common in children, so treatment target key symptoms
- If patient in severe depression, anxiety or acute agitation or aggression, hallucination, psychosis, mania and suicidal thoughts require urgent pharmacologic intervention.
- Decision to Use Psychoactive Medications with psychiatric symptoms in cancer patients is important part of their overall treatment.

CLASSES OF NEUROPSYCHOTROPIC MEDICATION



Psychotropic Prescribing Tips

- **Begin with low, go slow,** monitor efficacy, adverse reactions. Gradually increase the dose, and continue at a dose that produces adequate symptom control with minimum adverse reactions.
- **Monotherapy is ideal,** severe psychological disorders in childhood may require dual therapy
- **4-8 weeks is adequate trial** period to assess the efficacy of medication
- When prescribing antipsychotics in children, we must measure baseline parameters of waist and hip circumference, assessment of any movement disorders , nutritional status, and lipid profile
- Patient education (Psycho-education) is essential due to strong stigma against using psychotropic medication In treating pediatric mental illness

Pharmacokinetics in Pediatrics

- Most psychotropic medications are highly lipophilic
- The percentage of total body fat increases during the first year of life, then decreases gradually until puberty
- Toddlers and older children may have levels of these drug-metabolizing enzymes which exceed adult levels!
- In children medications have a more rapid renal clearance compared to adults
- Children may require higher mg/kg concentrations to achieve the same plasma levels
- CYP genes are the most important to neuropsychiatry: CYP 2D6, 2C9, 3A4, and 2C19.
- CYP 2D6 is main in the metabolism of psychiatric medications as Risperidone, Venlafaxine, Atomoxetine, Paroxetine.
- Poor CYP2C9 metabolizers who receive anti-depressants like Fluoxetine and Sertraline have higher risk of adverse effects, and lower doses from these medications are recommended.
- Sertraline and Escitalopram are quickly metabolised by children and twice daily dosing should be considered

Depression Disorder

- Manifest as sadness, feeling sad or irritable in sleeping or losing interest or pleasure in almost all activities for most of the day nearly every day for 2 weeks
- All children with depression should have ongoing psychotherapy as this has been shown to reduce suicidal thoughts and behaviors.
- If medications are indicated, begin with Escitalopram or Sertraline or Fluoxetine It is the only FDA approved SSRI for depression in children 8 and up.
- If Escitalopram does not work, consider switching to another SSRI: Sertraline or Fluoxetine according to their advantage
- Mirtazapine 7.5–15mg/day or tricyclic antidepressant like Amitriptyline 25mg/day have benefit in mild and comorbid depression
- If this still does not work or Major depressive disorder, consider switching to Venlafaxine.

Post traumatic stress disorders (PTSD).

- Manifest by Irritability, hopelessness and anhedonia, Lack of positive emotions may has nightmares and sleep problems scary thoughts and memories of a past event traumatic event.
- The AACAP guidelines treatment of PTSD discuss treatment with SSRIs, Second-generation antipsychotics, Mood stabilisers.
- SSRIs are well tolerated and efficacious in children with cancer, as first line pharmacologic treatment for healthy children and adolescents with depression, anxiety, post traumatic stress diorders (PTSD).
- Sedating anti-psychotic medications such as Risperdone, quetiapine and olanzapine may be useful to treat insomnia & sleep problems

Medication	Starting dose (mg)	Dose range (mg)
SSRI		
Sertraline	12.5–25	50–200 od
Citalopram	5–10	10–40 od
Tricyclic		
Imipramine	10	25–100*
Second-generation antipsychotic		
Risperidone	0.5	0.5–1 od
Quetiapine	25–50	50–200 od (at night)

Anxiety and Insomnia Disorders Treatment

- Children have an anxiety disorder such as general anexity disordes GAD, Separation Anxiety, Fear, worry or Social Phobia, Panic attacks
- NICE guidelines : suggest psychotherapy CBT and caution psychotropic medications are prescribed like SSRIs & SNRIs
- *Early and effective treatment may prevent continuity of psychopathology into adulthood*

Table 5.5 Typical dosage of medications for treatment of anxiety disorders in children and adolescents

Medication	Starting dose (mg)	Dose range (mg)
SSRI		
Sertraline	12.5–25	25–200 od
Fluoxetine	5–10	10–60 od
Fluvoxamine	12.5–25	50–200 (bd if >50)
Paroxetine	5–10	10–40 od
Citalopram*	5–10	10–40 od
SNRI		
Venlafaxine XR	37.5	37.5–225 od
Duloxetine	30	30–120 od
5-HT1A partial agonist		
Buspirone*	5 tds	15–60 od
Tetracyclic		
Mirtazapine*	7.5–15	7.5–30 at night
Benzodiazepine (prn)		
Clonazepam*	0.25–0.5	–

Anti depressant Choices for children

SSRI	Forms	Start Dose	+/- by	Max Dose	+RCT Evid.	FDA Approval
Escitalopram	Tab, liquid	5mg	5mg	20mg	Y	12-17
Fluoxetine	Tab, liquid	10 mg	5-10mg	60mg	Y	8-17
Sertraline	Tab, liquid	25mg	12.5-25mg	100mg	Y	N
Fluvoxamine	Tab, liquid	25mg BID	25mg	300mg	N	N

	pharmacotherapy for depression in children and adolescents
First line	Fluoxetine (FDA approved for 8 years and over in the USA)
Second line	Sertraline
Third line	Escitalopram (FDA approved for 12 years and over in the USA)
Fourth line	Consider augmentation of antidepressant with second-generation antipsychotic or mood stabilizer Consider mirtazapine

Anti depressant SSRIS Side Effects

- (TEAS) DURING INITIATION includes hypomania, agitation, anxiety, panic,insomnia
- Gastrointestinal disturbance (decreased appetite, nausea, diarrhea)
- Sexual dysfunction
- Autonomic (sweating)
- *Emotional flattening, cognitive slowing, and apathy.*
- Bruising and bleeding, with NSAIDS.
- SIADH (syndrome of inappropriate antidiuretic (hormone secretion)
- Decreased appetite and weight
- Dose-dependent increase in blood pressure, dry mouth,constipation .. ***SNRI***
- Seretonin syndrome in high doses
- Rare seizures , hypotension, hyponatremia , induction of mania, suicidality

How Anti-Depressant Drug Causes Side Effects

- Increases in serotonin concentrations at serotonin receptors in parts of the brain (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of serotonin in the gut causing diarrhea.
- ↑serotonin can cause diminished dopamine lead to emotional flattening , apathy.
- Dopamine reuptake blocking may contribute to Agitation, anxiety,
- In SNRI unwanted actions of norepinephrine on acetylcholine release causing constipation and dry mouth

What to Do About Side Effects

- Start low Go slow
- Wait for 3 weeks to adjust
- For GI upset, give med with a meal
- For(jitteriness, anxiety, insomnia).. Administer dose in the morning
- consider adding a 5HT2A antagonist(mirtazapine) for insomnia
- Consider a temporary dose reduction or gradual up-titration
- Consider switching to another antidepressant

Second Generation Antipsychotics SGA for children

Atypical Antipsychotics	Starting Daily Dose	Titration Dose ↑ q3–4 Day (~Min. Days to Antipsychotic Dose)	Usual Daily Dose Range for Aggression[a]		Usual Daily Dose Range for Psychosis	
			Child	Adolescent	Child	Adolescent
Clozapine	6.25–25 mg	1–2 × starting dose (18–20)	150–300 mg	200–600 mg	150–300 mg	200–600 mg[b]
Olanzapine	2.5 mg for children 2.5–5 mg for adolescents	2.5 mg (9–16)	No data available	No data available	7.5–12.5 mg	12.5–20 mg
Quetiapine	12.5 mg for children 25 mg for adolescents	25–50 mg to 150 mg, then 50–100 mg (18–33)	No data available	No data available	No data	300–600 mg
Risperidone	0.25 mg for children 0.50 mg for adolescents	0.5–1 mg (18–20 days)	1½–2 mg	2–4 mg	3–4 mg	3–6 mg

Drug	Starting dose**	Comment
Antipsychotics		
Aripiprazole	2 mg	Increase to 5–15 mg daily according to response
Clozapine	6.25–12.5 mg	Use plasma levels to determine maintenance dose
Olanzapine	2.5–5 mg	Use plasma levels to determine maintenance dose
Quetiapine	25 mg	Effective dose usually in the range 150–200 mg daily
Risperidone	0.25–2 mg	Adjust dose according to response and adverse effects

Anti Psychotic SGA Side Effects

- Abnormal movements, Rigidity (EPS, akathisia, parkinsonism)
- Abdominal pain ,Nausea, vomiting, salivary hypersecretion
- zombie-like syndrome of inattention, sedation, dizznes
- socialization and falling grades
- Increase appetite,Weight gain
- Dyslipidemia, Gynecomastia (boys)
- Hyperglycemia, Hyperprolactinemia, ketoacidosis, Galactorrhea/amenorrhea
- Reaction e Eosinophilia (DRESS) , Hematologic & oncologic: Neutropenia (6%)
- QT prolongation (Aripiprazole†, Risperidone, Olanzapine, Haloperidol, Quetiapine)
- Rare seizures
- Risk of tardive dyskinesia

Table 1.30 Antipsychotics – risk of diabetes and impaired glucose tolerance

Degree of risk	Antipsychotic drug
High	Clozapine, olanzapine
Moderate	Quetiapine, risperidone, phenothiazines
Low	High-potency FGAs (e.g. haloperidol)
Minimal	Aripiprazole, amisulpride, brexpiprazole, cariprazine, asenapine, lurasidone, ziprasidone

Drug	Sedation	Weight gain	Akathisia	Parkinsonism	Anti cholinergic	Hypotension	Prolactin elevation
Amisulpride*	–	+	+	+	–	–	+++
Aripiprazole	–	–	+	–	–	–	–
Olanzapine	++	+++	–	–	+	+	+
Quetiapine	++	++	–	–	+	++	–
Risperidone	+	++	+	+	+	++	+++
Haloperidol	+	+	+++	+++	+	+	++

How SGA Causes Side Effects

- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- Partial agonist actions at dopamine D2 receptors in the striatum can cause motor side effects, akathisia
- By blocking dopamine 2 receptor in striatum, may cause motor side effects, especially at high dose
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin
- By blocking histamine 1 receptors in the brain, it can cause sedation and possibly weight gain
- By blocking muscarinic 1 receptors, it can cause dry mouth, constipation, and sedation
- Partial agonist actions at serotonin 5HT1A receptors can cause nausea, occasional vomiting
- Mechanism of any possible weight gain is unknown
- Mechanism of any possible increased incidence of diabetes or dyslipidemia is unknown

What to Do About Side Effects

- Start with low doses and titrate slowly
- Usually best to give at night to reduce daytime side effects
- Often best to try another monotherapy trial of a different anti psych prior to augmentation
- Exercise and diet programs and medical management for high BMIs, diabetes, dyslipidemia
- For motor side effects: augmenting e' diphenhydramine or benztropine
- Reduce the dose, particularly for EPS, akathisia, sedation, and tremor
- For akathisia: reduce dose or add a beta blocker or benzodiazepine (5HT2A antagonist. (mirtazapine
- Consider a temporary dose reduction or a more gradual up-titration
- switching to other antipsychotic

Attention Deficit Hyperactivity Disorder (ADHD)

- Manifest by trouble paying attention, controlling impulsive behaviors hyperactive (may act without thinking about what the result will be)
- Medications Can help greatly improving quality of life by affecting the ability to increasing focus sand attention , decrease physical hyperactivity
- Combination of medications and behavioral interventions have been shown as a superior treatment to either alone

A) For attention deificiency

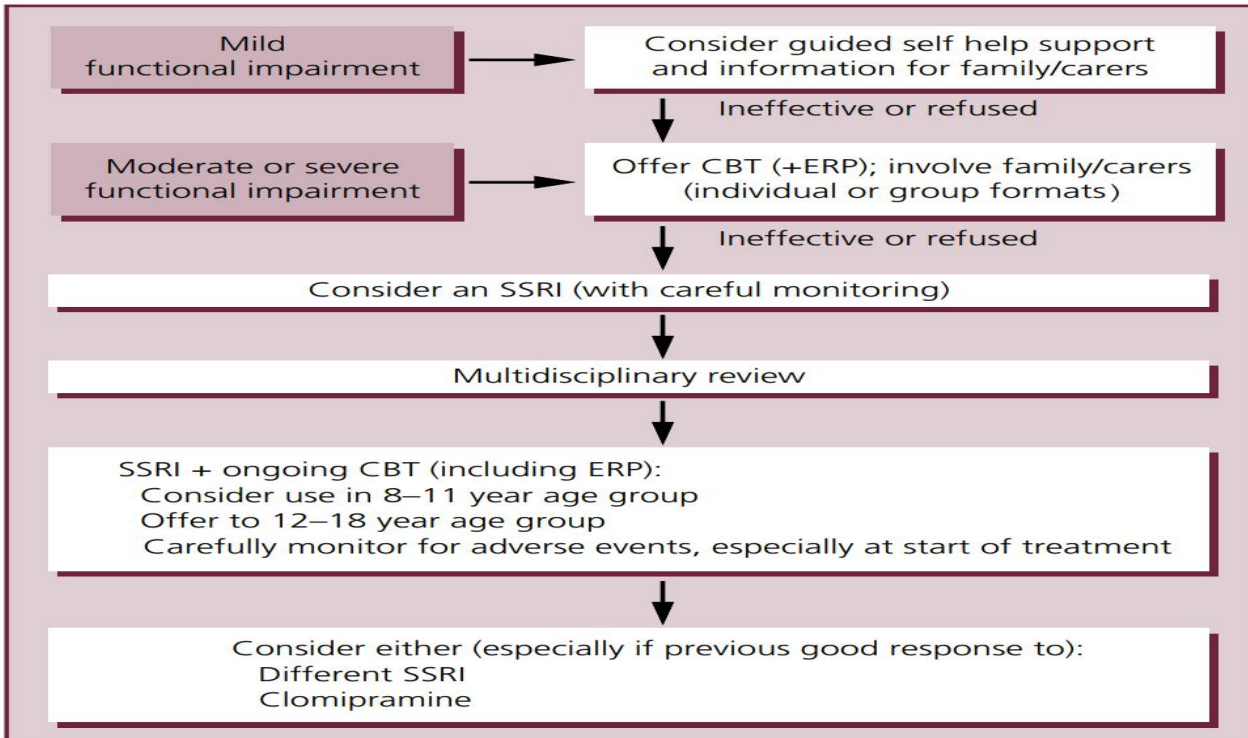
- Natural products enhancing memory : Omega 3 , Ginko biloba
- Non-Stimulant :
- Atomoxetine: : 0.5mg/kg/day, up to 1.4mg/kg/day
- Stimulant :
- Methylphenidate (Concerta) :Initially 18 mg in the morning, titrated up to 54 mg daily is usually first line when a drug is indicated

B) For Hyperactivity

- Sedating anti-psychotic medications such as Risperdone, quetiapine and olanzipine , Aripiprazole useful to treat hyperactivity

Obsessive Compulsive Disorder

- CBT is effective in this patient group and is the treatment of first choice although it may be combined with medication.
- The UK, NICE guidelines recommend that if a young person has responded to medication, treatment should continue for at least 6 months after remission.
- FDA approved medications for treatment of OCD
  - Sertraline $\geq$ 6 y/o
  - Fluvoxamine $\geq$ 8 y/o
  - Fluoxetine $\geq$ 7 y/o



Pediatric Bipolar Disorder

- Controversial diagnosis Short-lived episodes of both major depression and mania. (severe irritability, conduct, emotional instability, and severe temper outbursts)
- Psychosocial interventions CBT are necessary in addition to medications
- NICE guidelines suggest : second-generation antipsychotics (SGA) may be used as first-line treatment, and mood stabilisers (MS) can be added after failure of two trials of SGA.
- Approved Medications by FDA for manic and mixed states in ages 10-17: Quetiapine, Risperidone, Aripiprazole, Olanzapine approved≥13yrs.
- AEDs as Mood stabilizer: Carbamazepine, Valproic acid , topiramate and oxcarbazepine in monotherapy or as augmentation
- Antidepressants SSRIs should be used with care and only in the presence of an antimanic agent

for acute mania*

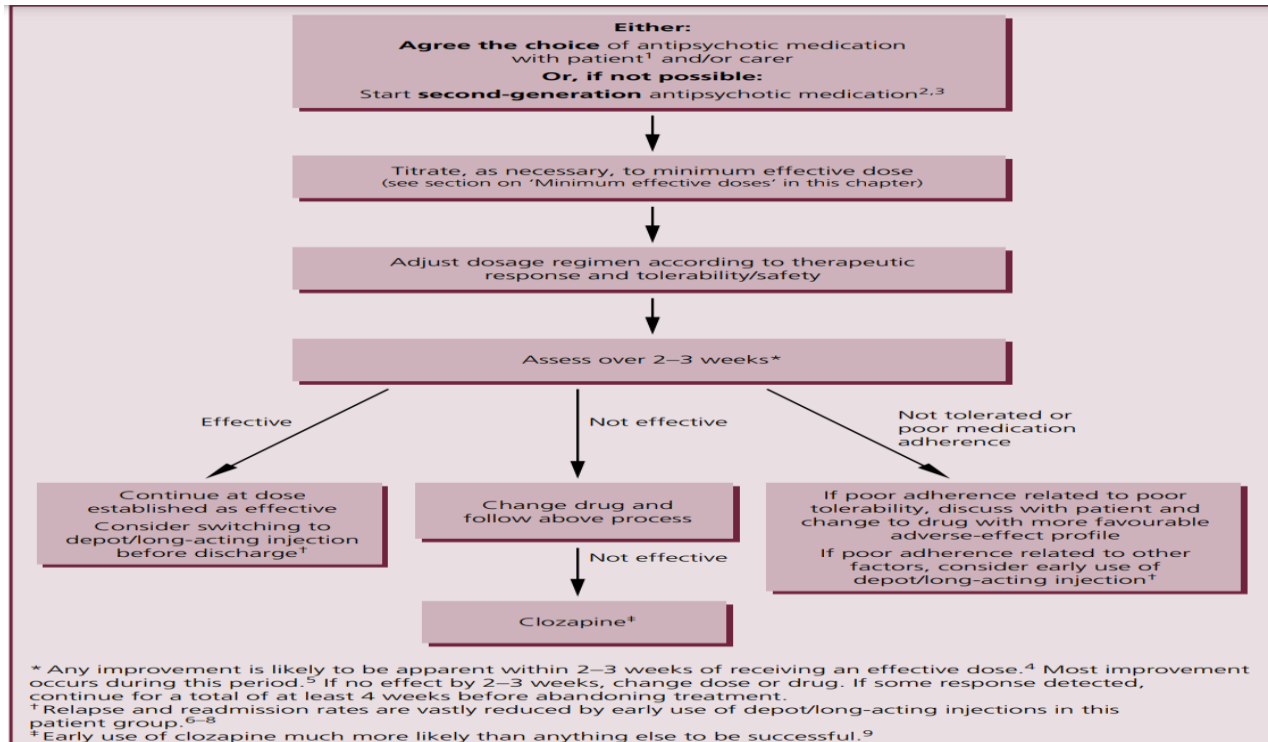
Drug	Dose
Aripiprazole	10 mg daily
Olanzapine	5–20 mg daily
Quetiapine	Up to 400 mg daily
Risperidone	0.5–2.5 mg daily

Table 5.4 Recommended first-line treatments for bipolar depression*

Drug	Dose
Olanzapine/fluoxetine	6/25–12/50 mg daily
Quetiapine	Up to 300 mg daily

Psychosis in children and adolescents

- Psychosis, visual or audiatory hallucination, delusions (a false, fixed, odd belief)
- NICE recommends oral antipsychotics in conjunction with family interventions and individual CBT.
- First-generation antipsychotics: Haloperidol in emergency cases
- Second-generation antipsychotics in EOSS disorder: Olanzapine risperidone, aripiprazole, quetiapine



Oppositional & Behavioral Disorder

- Pattern of anger, irritability, arguing and opposition to rules and norms for socially acceptable behaviour toward peers, parents.
- No official medications approved by FDA for treatment
- Best evidence is psychopharmacology and psychotherapy (CBT, family) and psychosocial behavioral interventions
- Medications often used to treat related symptoms, such Aggression
- Mood stabilizers (Oxcarbazepine, Valproic acid)
- Atypical Antipsychotics used as well (Risperidone, Aripirazole, olanzapine, Queitiapine)
- Stimulants Off-label use (Atomoxetine)

Autism Spectrum Pharmacotherapy

- Developmental disability have problems with social communication and interaction, and restricted or repetitive behaviors or interests.
- NO medications approved for core symptoms
- Medications often used to treat related symptoms, such as depression, anxiety, and aggression
- Children with ASD have significant Aggression &irritability & sleep problems : (SGAs) Aripiprazole & Risperidone is FDA approved
  - Methylphenidate, Clonidine and have preliminary data
- Restricted repetitive behaviours and Anxiety: often use SSRIs, at low doses
- Patients with autism are often very sensitive to adverse effects, even at low doses

Doses of risperidone in paediatric patients with autism spectrum disorders (by total mg/day)

Weight categories	Days 1–3	Days 4–18	Increments if dose increases are needed	Dose range
<20 kg*	0.25 mg	0.5 mg	+0.25 mg at ≥2 week intervals	0.5–3 mg**
≥20 kg	0.5 mg	1.0 mg	+0.5 mg at ≥2 week intervals	1.0–3 mg***

Tics and Tourette's syndrome

- children defined by persistent motor and vocal tics occur in 5–20%
- Co-morbid OCD, ADHD, depression, anxiety and behavioural problems are more prevalent than would be expected by chance, and often cause the major impairment in people with tic disorders.
- Most people with tics do not require pharmacological treatment; education and behavioural programs, for the individual with tics, their family and surrounded people
- Second-generation antipsychotics (SGAs) : Aripiprazole , quetiapine and olanzapine is an effective and well-tolerated treatment of children with TS
- Baclofen was suggestive of beneficial effects in overall impairment rather than a specific effect on tics.
- Case reports or case series describing positive effects for Clonidine, ondansetron, tramadol, pregabalin have been published.

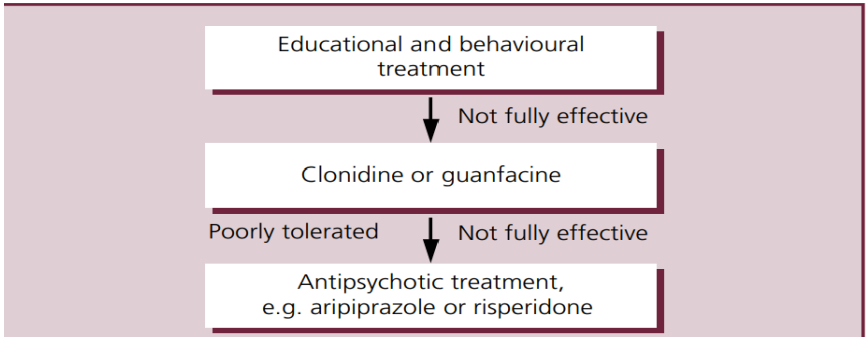


Table 5.9 Starting doses of commonly used psychotropic drugs in children and adolescents[1,2]*

Drug	Starting dose**	Comment
Antipsychotics		
Aripiprazole	2 mg	Increase to 5–15 mg daily according to response
Clozapine	6.25–12.5 mg	Use plasma levels to determine maintenance dose
Olanzapine	2.5–5 mg	Use plasma levels to determine maintenance dose
Quetiapine	25 mg	Effective dose usually in the range 150–200 mg daily
Risperidone	0.25–2 mg	Adjust dose according to response and adverse effects
Antidepressants		
Fluoxetine	5–10 mg/day	Adjust dose according to response and adverse effects
Sertraline	25–50 mg daily	Effective dose 50–100 mg, sometimes higher
Citalopram	10 mg daily	Effective dose 10–40 mg (note QT effects)
Escitalopram	5 mg daily	Effective dose 10–20 mg (note QT effects)
Other drugs		
Lithium	100–200 mg/day lithium carbonate	Use plasma levels to determine maintenance dose
Valproate	10–20 mg/kg/day in divided doses	Use plasma levels to determine maintenance dose. Avoid use in females of child-bearing age

Refrences

- https://www.bap.org.uk/guidelines
- https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines
- https://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Home.aspx
- https://dl.uswr.ac.ir/bitstream/Hannan/32636/1/9781119442608.pdf
- https://www.cambridge.org/core/books/stahls-essential-5th.ed psychopharmacology
- https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines
- https://www.academia.edu/13581055/Psychopharmacology_in_Psycho_oncology
- https://www.wpanet.org/psycho-oncology-and-palliative-care
- https://iacapap.org/_Resources/Persistent/bd5ed920e764a942a252495e744072214f773c69/I.6-PSYCHOONCOLOGY-2019.01.pdf