# مدیریت عوارض درمان های اختلال خلقی دو قطبی در کودکان و نوجوانان

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# In general

- The risks and benefits of medication for bipolar disorder in children and adolescents need careful consideration with the family and young person.
- If medication is commenced, the principle is to ‘start low, go slow’, with closer monitoring than in adults
- Medication should be prescribed in a psychosocial therapeutic framework.
- Bipolar disorder affects numerous developmental processes, including academic, social and family functioning therefore treatment needs to be multimodal

# Lithium

# Lithium side effects

- younger children tend to experience higher rates of side-effects with lithium administration than adolescents
- Side-effects may be particularly common in children under age six, correlating with higher serum levels, higher dose per kilogram, and early phase of treatment

# Common side effects of Lithium

- Polyuria
- Polydypsia
- Tremor
- weight gain
- Nausea

- Diarrhea
- Hypothyroidism
- cognitive dulling
- Sedation
- leukocytosis

# Side effects of lithium

- Cardiac: Bradycardia and cardiac arrhythmias, Brugada syndrome
- Before starting lithium treatment, clinicians should ask about known heart conditions, unexplained fainting, and family history of problems or sudden unexplained death before age 45
- GI effects: nausea, decreased appetite, vomiting, and diarrhea
- can be diminished by dividing the dosage, administering the lithium with food, or switching to another lithium preparation
- Some lithium preparations contain lactose, which can cause diarrhea in lactose-intolerant persons.

# Lithium induced tremor

- A lithium-induced postural tremor may occur that is usually 8 to 12 Hz and is most notable in outstretched hands
- The tremor can be reduced by dividing the daily dosage, using a sustained-release formulation, reducing caffeine intake, reassessing the concomitant use of other medicines, and treating comorbid anxiety.
- β-Adrenergic receptor antagonists and primidone reduce the tremor.
- In persons with hypokalemia, potassium supplementation may improve the tremor.
- When a person taking lithium has a severe tremor, the possibility of lithium toxicity should be suspected and evaluated

# Renal effects

- The most common adverse renal effect of lithium is polyuria with secondary polydipsia.
- When polyuria is a significant problem, the person's renal function should be evaluated and followed up with 24-hour urine collections for creatinine clearance determinations.
- Treatment consists of fluid replacement, the use of the lowest effective dosage of lithium, and single daily dosing of lithium.
- Treatment can also involve the use of a thiazide or potassium-sparing
- If treatment with a diuretic is initiated, the lithium dosage should be halved, and the diuretic should not be started for 5 days because the diuretic is likely to increase lithium retention

# Thyroid side effects

- Lithium causes a generally benign and often transient diminution in the concentrations of circulating thyroid hormones.
- Persons taking lithium to treat bipolar disorder are twice as likely to develop hypothyroidism if they develop rapid cycling.
- About 50% of persons receiving long-term lithium treatment have laboratory abnormalities, such as an abnormal thyrotropin-releasing hormone response, and about 30% have elevated concentrations of thyroid-stimulating hormone (TSH).
- If symptoms of hypothyroidism are present, replacement with levothyroxine is indicated.
- In lithium-treated persons, TSH concentrations should be measured every 6 to 12 months.

# Lithium side effects

- Cognitive effects: lithium use has been associated with dysphoria, lack of spontaneity, slowed reaction times, and impaired memory.
- They are a frequent cause of noncompliance.
- The differential diagnosis should include depressive disorders, hypothyroidism, hypercalcemia, other illnesses, and other drugs.
- Some, but not all, persons have reported that fatigue and mild cognitive impairment decrease with time.

# Lithium side effects

- Patients taking lithium should be advised that changes in the body's water and salt content
- Excessive sodium intake lowers lithium concentrations.
- Conversely, too little sodium can lead to potentially toxic concentrations of lithium.
- Decreases in body fluid (e.g., excessive perspiration) can lead to dehydration and lithium intoxication.
- Patients should report whenever medications are prescribed by another clinician because many commonly used agents can affect lithium concentrations.

# Lithium side effects

- Weight gain: results from a poorly understood effect of lithium on carbohydrate metabolism.
- Weight gain can also result from lithium-induced hypothyroidism, lithium-induced edema, or excessive consumption of soft drinks and juices to quench lithium-induced thirst.

# Lithium side effects

- NSAIDS, marijuana, alcohol: increase Li levels
- Caffeine lowers Li levels
- Obtain blood levels 4-5 days after dose changes
- Once achieving a stable lithium dose, lithium levels and renal and thyroid function tests, every 3–6 months, are warranted

# Lithium side effects

- Dermatologic effects: may be dose dependent.
- They include acneiform, follicular, and maculopapular eruptions; pretibial ulcerations; and worsening of psoriasis.
- Alopecia has also been reported.
- Persons with many of those conditions respond favorably to changing to another lithium preparation and the usual dermatologic measures.
- Lithium concentrations should be monitored if tetracycline is used

# Lithium toxicity

- Narrow therapeutic window: blood levels 0.6-1.2 mEq/L
- Has low therapeutic damage with permanent renal and neurologic damage
- An inability to appropriately monitor blood levels precludes the use of lithium

# lithium toxicity

- Mild lithium toxicity may be associated with gastrointestinal distress and dizziness
- Resolve with increased hydration and correcting the underlying process
- Severe toxicity may require admission to the hospital for hydration

# Lithium Toxicity and Overdoses

- The early signs and symptoms of lithium toxicity include:
- Neurologic symptoms, such as coarse tremor, dysarthria, and ataxia
- GI symptoms; cardiovascular changes; and renal dysfunction
- Risk factors include exceeding the recommended dosage, renal impairment, low sodium diet, drug interaction, and dehydration.
- Children experiencing fever from a viral illness or other infection are particularly at risk for dehydration and subsequent lithium toxicity.

# Lithium toxicity

- lithium should be stopped and dehydration treated.
- Unabsorbed lithium can be removed from the GI tract by ingestion of sodium polystyrene sulfonate (Kayexalate) or polyethylene glycol solution, but not activated charcoal.
- Ingestion of a single large dose may create clumps of medication in the stomach, which can be removed by gastric lavage with a wide-bore tube.
- The value of forced diuresis is still debated.
- In severe cases, hemodialysis rapidly removes excessive amounts of serum lithium. Postdialysis serum lithium concentrations may increase as lithium is redistributed from tissues to blood, so repeat dialysis may be needed.
- Neurologic improvement may lag behind clearance of serum lithium by several days because lithium crosses the blood–brain barrier slowly.

# Lithium+depression

- When a depressive episode occurs in a person taking maintenance lithium, the differential diagnosis should include:
- lithium-induced hypothyroidism
- substance abuse
- lack of compliance with the lithium therapy.

- Possible treatment approaches include:
- increasing the lithium concentration (up to 1 to 1.2 mEq/L)
- adding supplemental thyroid hormone (e.g., 25 µg a day of liothyronine [Cytomel]) even in the presence of normal findings on thyroid function tests
- augmentation with valproate or carbamazepine, the judicious use of antidepressants, or electroconvulsive therapy (ECT).
- After the acute depressive episode resolves, other therapies should be tapered off in favor of lithium monotherapy, if clinically tolerated

# Sodium valproate

# Sodium Valproate side effect

- The two most serious adverse effects of valproate treatment affect the pancreas and liver.
- Risk factors for potentially fatal hepatotoxicity include:
- 1-young age (younger than 3 years)
- 2- concurrent use of phenobarbital
- 3- the presence of neurologic disorders especially inborn errors of metabolism.
- Rare, idiosyncratic event

# Valproate hepatotoxicity

- A modest increase in liver function test results does not correlate with the development of serious hepatotoxicity.
- if symptoms of lethargy, malaise, anorexia, nausea and vomiting, edema, and abdominal pain occur in a child treated with valproate, the clinician must consider the possibility of severe hepatotoxicity

# Sodium Valproate Pancreatitis

- Rare cases of pancreatitis have been reported
- They occur most often in the first 6 months of treatment, and the condition occasionally results in death.
- Pancreatic function can be assessed and followed with serum amylase concentrations.
- Asymptomatic amylase not predictive

# Polycystic Ovarian Syndrome (PCOS)

- PCOS is characterized by polycystic ovaries, hyperandrogenism, and chronic anovulation.
- Clinical manifestations include hirsutism, alopecia, acne, and menstrual abnormalities.
- Laboratory abnormalities include chronically elevated plasma testosterone, increased LH secretion, and low or normal plasma FSH levels

# Valproate side effects

- Teratogenicity: Neural tube defect: 1–4% with valproate
- Preconceptual education and folate supplementation for all young women of childbearing potential
- Thrombocytopenia: Decrease dose if clinically symptomatic (i.e., bruising, bleeding gums)
- Thrombocytopenia more likely with valproate levels ≥110 µg/mL (women) and ≥135 µg/mL (men)

# Valproate side effects

- GI side effects: nausea, vomiting, dyspepsia, and diarrhea.
- most common in the first month of treatment, particularly if the dosage is increased rapidly.
- Unbuffered valproic acid (Depakene) is more likely to cause GI symptoms than the enteric-coated “sprinkle” or the delayed-release divalproex sodium formulations.
- CNS side effects: sedation, ataxia, dysarthria, and tremor.
- Valproate-induced tremor may respond well to treatment with β-adrenergic receptor antagonists or gabapentin.
- Treatment of the other neurologic adverse effects usually requires lowering the valproate dosage

# Valproate side effects

- Weight gain is a common adverse effect, especially in long-term treatment, and can best be treated by strict limitation of caloric intake.
- Hair loss may occur in 5% to 10% of all persons treated
- Rare cases of complete loss of body hair
- Treatment of valproate-associated hair loss with vitamin supplements that contain zinc and selenium.

# Valproate side effects

- High dosages of valproate (above 1,000 mg a day) may rarely produce mild to moderate hyponatremia
- It is reversible upon lowering of the dosage.
- Overdoses of valproate can lead to coma and death.

# Valproate interaction

- Asymptomatic elevation of transaminase concentrations up to three times the upper limit of normal are common, do not require any change in dosage.
- monitoring every 1–2 weeks; if stable and patient is responding to valproate, results are monitored monthly to every 3 months
- Pronounced transaminase elevation (more than three times normal): dosage reduction or discontinuation of valproate
- increase dose or rechallenge if transaminases normalize and if the patient is a valproate responder

# Valproate interaction

- Valp+lit: is the exacerbation of drug-induced tremors, which can usually be treated with β-receptor antagonists.
- Valp+ DRAs: increased sedation
- Increased severity of extrapyramidal symptoms which usually responds to treatment with antiparkinsonian drugs.
- Valproate can usually be safely combined with carbamazepine or SDAs

# Valproate interaction

- Valp+ lamogel: Valproate more than doubles lamotrigine concentrations, increasing the risk of a serious rash (Stevens–Johnson syndrome, and toxic epidermal necrolysis).
- Valp+Antidepressants: Amitriptyline and fluoxetine may increase valproate serum concentrations
- Valp+Clonazepam: Absence status (rare; reported only in patients with pre-existing epilepsy)

# DOSAGE AND CLINICAL GUIDELINES

- A baseline hepatic panel, complete blood cell and platelet counts, and pregnancy testing
- Additional testing: amylase and coagulation studies if baseline pancreatic disease or coagulopathy is suspected.
- Hepatic transaminase concentrations should be obtained 1 month after initiation of therapy and every 6 to 24 months thereafter.

# Atypical Antipsychotics

# Atypical APs

- Of the atypicals, only four are approved by the U.S. Food and drug administration (FDA) for use in pediatric patients: aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone.
- Children appear to be at greater risk of developing eps than adults.
- Frequently associated with fairly significant weight gain

# Antipsychotics

- Children are not “little adults” and the effects of psychotropic agents on developing systems—particularly the neuronal systems—differ from the effects in adults
- Agents that are effective in adults may not be effective in pediatric patients
- It appears that children and adolescents are at higher risk than adults for antipsychotic-induced hyperprolactinaemia, weight gain and, possibly, associated metabolic abnormalities

# Risperidone

- The EPS of risperidone are largely dosage dependent, and there has been a trend to using lower doses than initially recommended.
- Weight gain, anxiety, nausea and vomiting, rhinitis, erectile dysfunction, orgasmic dysfunction, and increased pigmentation are associated with risperidone use.

# Risperidone

- The most common drug-related reasons for discontinuation of risperidone use are EPS, dizziness, hyperkinesias, somnolence, and nausea.
- Marked elevation of prolactin may occur.
- Weight gain occurs more commonly with risperidone use in children in

# Olanzapine

- Other than clozapine, olanzapine consistently causes a greater amount and more frequent weight gain than other atypicals.
- This effect is not dose related and continues over time.
- Clinical trial data suggest it peaks after 9 months, after which it may continue to increase more slowly.

# Olanzapine

- Somnolence, dry mouth, dizziness, constipation, dyspepsia, increased appetite, akathisia, and tremor are associated with olanzapine use.
- A small number of patients (2%) may need to discontinue use of the drug because of transaminase elevation.
- There is a dose-related risk of EPS.
- The manufacturer recommends “periodic” assessment of blood sugar and transaminases during treatment with olanzapine.

# Quetapine

- Somnolence, postural hypotension, and dizziness are the most common adverse effects of quetiapine.
- These are usually transient and are best managed with initial gradual upward titration of the dosage.
- Quetiapine is the SDA least likely to cause EPS, regardless of dose.

# QUETIAPINE

- When used at higher doses, serial electrocardiograms should be performed.
- Despite its short elimination half-life, quetiapine can be given to many patients once a day.
- This is consistent with the observation that quetiapine receptor occupancy remains even when concentrations in the blood have markedly declined.
- Quetiapine in doses of 25 to 300 mg at night has been used for insomnia.

# Quetiapine

- Phenytoin increases quetiapine clearance fivefold, no major pharmacokinetic interactions have been noted.
- The FDA has added a new warning about quetiapine cautioning prescribers about potential prolongation of the QT interval when above-recommended amounts of quetiapine are combined with specific drugs.

# Quetiapine

- Quetiapine should be avoided in circumstances that may increase the risk of occurrence of torsade de pointes and/or sudden death including:
- (1) a history of cardiac arrhythmias such as bradycardia
- (2) hypokalemia or hypomagnesemia
- (3) concomitant use of other drugs that prolong the QTc interval
- (4) presence of congenital prolongation of the QT interval.
- Postmarketing cases also show increases in QT interval in patients who overdose

# Quetiapine

- Prolactin elevation is rare and both transient and mild when it occurs.
- Quetiapine is associated with modest transient weight gain in some persons, but some patients occasionally gain a considerable amount of weight.
- Small increases in heart rate, constipation, and a transient increase in liver transaminases may also occur.

# Aripiprazole

- Absorption is not affected by food
- relatively long half-lives make aripiprazole suitable for once-daily dosing
- Lithium and valproic acid do not affect the steady-state concentrations of aripiprazole.
- The most commonly reported side effects of aripiprazole are headache, somnolence, agitation, dyspepsia, anxiety, and nausea
- Aripiprazole is an a1-adrenergic receptor antagonist, which may cause some patients to experience orthostatic hypotension

# aripiprazole

- The absence of complete D2 blockade in the striatal areas would be expected to minimize EPS
- Aripiprazole does cause akathisia-like activation.
- Insomnia is another common complaint.
- Weight gain or diabetes mellitus has not an increased incidence
- Prolactin elevation does not typically occur.
- Does not cause significant QTC interval changes.
- There have been reports of seizures.

# Management of side effects

- Provide adequate information to patients and family in deciding treatment choice
- Family preference should be considered while choosing Antipsychotics
- Start with low dose and monitor the dose depending on response
- Poly pharmacy should be used in case of nonresponse with monotherapy.
- Indicated adequate trial period with one drug should be given before changing the medication.
- Review the dose of drug and side effect profile regularly


HAVE A NICE DAY