Paediatric Psychopharmacology.

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Childhood pharmacokinetics

- Children have greater hepatic capacity
- More glomerular filtration
- Less fatty tissue
- Less ability to store drugs in their fat
- Due to quick elimination, half lives are shorter.
- Stimulants, antipsychotics and tricyclic drugs eliminated more rapidly.

Principles of prescribing

- Target symptoms, not diagnoses.
- ‘off- label’ use, or unlicensed medications are often necessary in paediatric practice.
- Begin with less, go slow and be prepared to end with more.
- Multiple medications are often required in the severely ill.
- Allow time for an adequate time of treatment.
- Where possible, change one drug at a time.

Autistic spectrum disorders.

- Core deficits in 3 areas.
- Language, social interaction,behaviour (stereotypies, restricted, unusual patterns of interest)
- Comorbidity with mental retardation, ADHD, epilepsy, anxiety, OC features, mood disorders,self harm, irritability, aggression, sleep disurbances.

ASD...

- Response to medications may be less robust,higher incidence of adverse effects.
- Conservative dosing and titration of doses.
- Key studies: research units on pediatric psychopharmacology autism network- Risperidone trials
- Research units on pediatric psychopharmacology Autism network – Methylphenidate Trial.

Adhd symptoms in ASD

- As per RUPP Autism Network, and Santosh et al: positive benefits of methylphenidate.
- Variable responses in children with ASD and adhd symptoms.
- Either marked improvement with few side effect or poor response with problematic side effects.
- Limited efficacy in this group

ASD with adhd symptoms

- Low doses ie 0.125mg/kg, with small increments.
- Stop immediately if behaviour deteriorates, or unacceptable side effects.
- Small open label trials show Atomoxetine may be useful, RCTs awaited.
- May be more effective in milder ASD symptoms.
- Some evidence for risperidone, clonidine.
- None for anticonvulsants, SSRI, benzodiazepines.

Irritability in ASD (aggression, tantrums, self injurious behaviour)

- Duration of treatment is around 6-12 months
- FDA approved are risperidone and Aripiprazole.
- Recent meta-analysis of short term aripiprazole and children 6-17 years , found a significant reduction in irritability with a moderate effect size.
- Cochrane review say it is useful in managing irritability, hyperactivity and stereotypies and children with ASD, but has side effects of weight gain, sedation, sialorrhoea and EPS.

Irritability in ASD (aggression, tantrums, self injurious behaviour)

- Recommended dose is 5-15mg.
- Effectiveness of olanzapine and Ziprasidone not tested in powered RCTs.
- Some data shows combination of risperidone and topiramate is better than risperidone alone.
- Mood stabilizers not as effective as SGAs for irritability in ASD.

Restricted repetitive behaviours and interests domain.

- Important treatment target to improve overall outcomes in ASD.
- Behavioural therapies are first line.
- Severe behaviours, impacting education, social performance, risk to others and self harm should be treated.
- SSRI's studied are fluoxetine, sertraline, fluvoxamine, citalopram and escitalopram.

RRBI's

- Inconsistent benefits from SSRI's.
- Side effects of increased activation and agitation.
- Start with 2.5mg fluoxetine, with mean dose being 10mg.
- Clomipramine has modest effectiveness.
- Others: Risperidone, anticonvulsants, and neuropeptide Oxytocin.

Social and communication impairment

- No drug shown to improve core social and communication impairment.
- Risperidone has a secondary effect through improvement in irritability.
- Most promising: glutamatergic drugs and oxytocin

Sleep disturbance in ASD

- Melatonin effective, as per 17 studies.
- Doses range from 1-10mg.
- Well tolerated
- Risperidone may benefit in those with extreme irritability.
- If child is anxious/depressed, antidepressants.
- If due to hyperarousal,then clonidine or clonazepam.

Pathologic aggression in ASD

- It may be severe, destructive,chronic and unresponsive to psychosocial interventions.
- Need to understand what drives the aggression.
- As per Barzman and Findling, medications to be used only if
- Current treatments not helping
- Underlying conditions adequately treated
- All behavioural and psychological methods not helping to ensure safety.

Pathologic aggression in ASD.

- Most common comorbidity is bipolar disorder, psychosis, and LD.
- No data for children less than 5 years of age.
- Most evidence for risperidone in aggression.
- Fewer data for olanzapine, quitepine, aripiprazole, and clozapine.

Pathologic aggression in ASD.

- Recent systematic review highlights importance of safety monitoring.
- SGAs cause weight gain, metabolic and hormonal imbalance.
- Weight gain worse in children than adults.
- Moodstabilizers lithium and sodium valproate effective in aggression.

Psychosis in Children & Adolescents.

- Onset of schizophrenia is rare prior to 13 years of age, it increases in adolescence .
- 3 major RCTs with FGAs.
- High rates of EPS, treatment emergent dyskinesias, and sedation.
- Should be avoided in children.
- Many RCTs for SGAs in EOSS.
- Olanzapine, risperidone , aripiprazole effective in psychosis treatment.
- Some evidence for quetiapine, but some safety concerns for Ziprasidone.

Psychosis...

- This population more prone to neutropenia and seizures from clozapine, than adults.
- NICE recommends oral antipsychotics, family interventions and individual CBT.

Drug treatment of psychosis.

First choice	Allow patient to choose from
	Aripirazole (to 10mg)
	Olanzapine (to 10mg)
	Risperidone (to 3mg)
Second choice	Switch to alternative from list above
Third choice	Clozapine

Anxiety disorders in children and adolescents.

- Fear and worry are common and normal in children.
- But Anxiety disorders begin in childhood.
- Most common with overall prevalence 8%-30%.
- Exclude other diagnoses.

Anxiety disorders

- SSRIs treatment of choice in moderate to severe anxiety
- Several RCTs have shown benefit in GAD,social phobia,seraration anxiety disorder,selective mutism.
- Consider trial of stopping meds after 1 year of no symptoms.

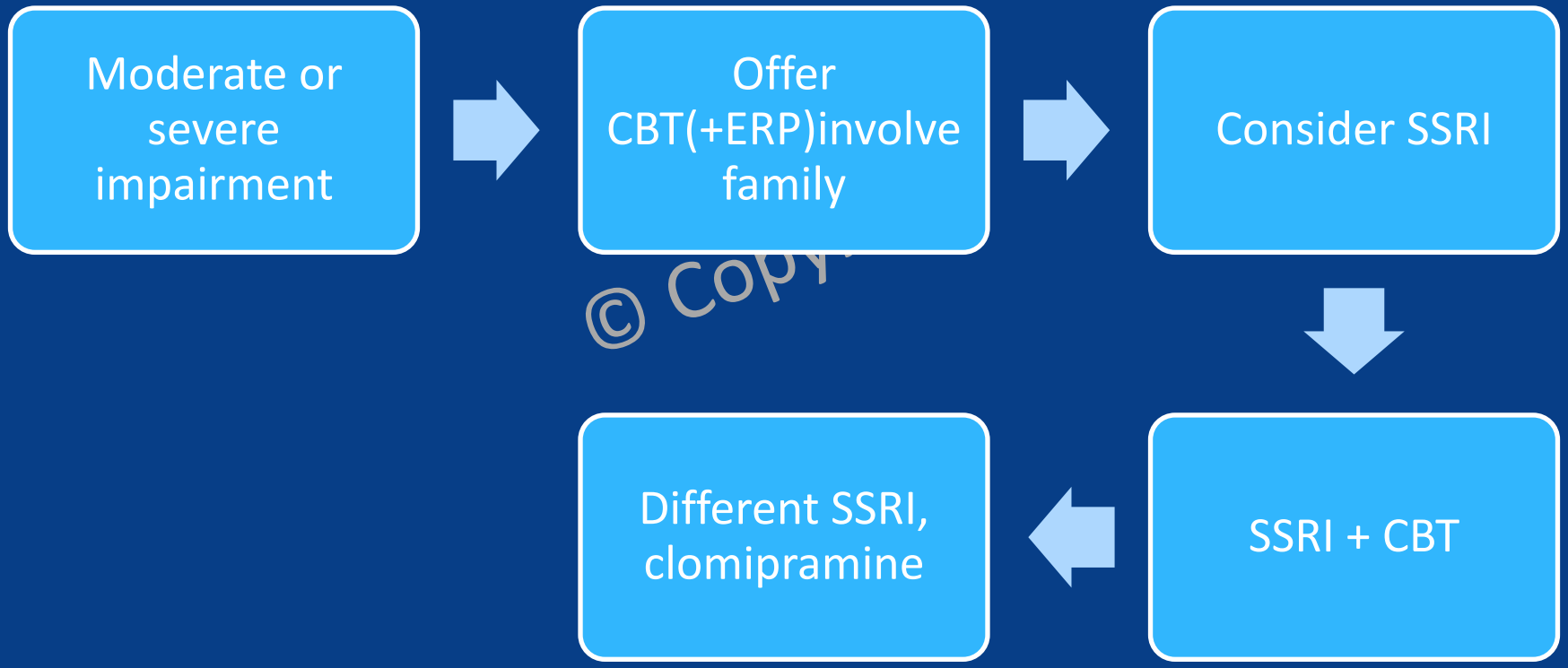
Anxiety disorders

- Venlafaxine tested in 2 RCTs with RR of response of 1.46 over placebo.
- Can be considered 2nd line, when SSRIs ineffective.
- Open label studies suggest buspirone and mirtazepine may be useful, though efficacy not known.
- Benzodiazepines may potentiate initial SSRIs, but not advisable.

Anxiety disorders

- AACAP, NICE and Maudsley guidelines recommend psychotherapy in mild anxiety disorders.
- Multimodal treatment of psycho-education, exposure based CBT and only if no/partial response, to add medications.
- Always start at low doses and titrate at regular intervals, monitoring for side effects.
- For preschoolers, no RCTs done, but case reports suggest benefit with fluoxetine and buspirone.

Obsessive compulsive disorders in Children



OCD in children

- POTS (pediatric OCD treatment study)
- FDA approved fluvoxamine, fluoxetine,sertraline , Clomipramine.
- Begin with CBT, later combine with an SSRI.
- Refractory OCD in children: 1/4th don't respond
- risperidone,(off label) augmentation.
- Ketamine and riluzole are not effective in children.

Posttraumatic stress disorder.

- Trauma focussed CBT
- EMDR (eye movement desensitization and reprocessing.
- CBITS (cognitive behavioural for trauma in schools)
- SPARCS (structured psychotherapy for Adolescents responding to chronic stress)

PTSD…..

- TARGET (Trauma affect regulation: guide for education and therapy.)
- Crisis Intervention /Psychological Debriefing

PTSD….

- Alpha-2 agonists ie clonidine for dysregulation of the noradrenergic system
- Beta- antagonists propranolol, improves hyperarousal and intrusive thoughts
- Clonidine may reduce reenactment symptoms in children
- In young children withhyperarousal, impulsivity and agitation show improvement with clonidine 0.05-0.1 mg.

PTSD…

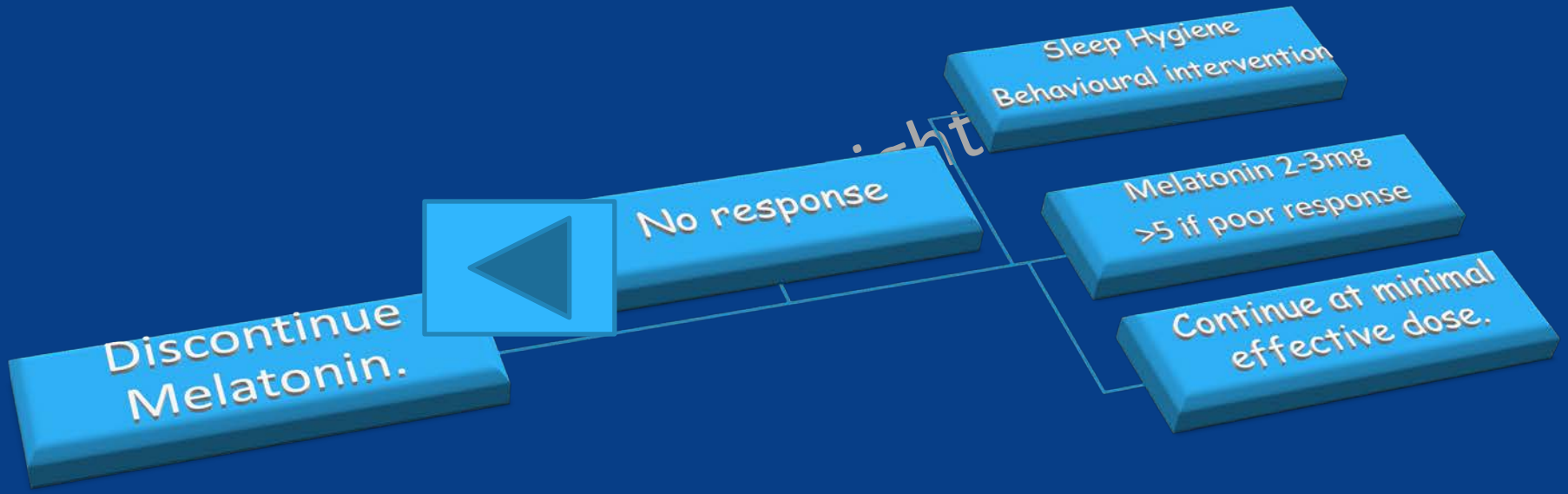
- Due to comorbidity with depressive disorders, anxiety disorders,behavioural problems, multitude of medications used to ameliorate symptoms of PTSD.
- FDA approved is Sertraline and Paroxetine in adults, scant evidence for its use in the youth.
- No superiority of sertraline and citalopram over placebo, in several trials.
- In PTSD with burns, SSRIs found effective.

PTSD….

- SGAs like risperidone, olazapine, quetiapine, ziprasidone,and aripiprazole studied with mixed results in adults.
- Risperidone and aripiprazole tried in children
- Carbamazepine and valproex have been used in some trials, with some improvement with higher doses.
- Benzodiazepines given, but no controlled trials.
- For comorbid depression, anxiety, SSRIs recommended.

Use of melatonin in Insomnia in children

Melatonin.


Sleep Hygiene
Behavioural intervention
Melatonin 2-3mg
>5 if poor response
Continue at minimal effective dose.
No response
Discontinue Melatonin.

Conduct Disorder

- Many diagnoses complicated by aggressive and oppositional tendencies.
- Comorbid disorders should be the primary target of pharmacotherapy.

Conduct disorder..

- Moodstabilizers ie divalproex sodium, lithium.
- Antipsychotics esp. atypical antipsychotics.
- Stimulants.
- Dysphoric aggression more responsive than predatory aggression, to medications.

Oopositional Defiant disorder.

- Mostly comorbid with ADHD, substance use, delinquency.
- Recent trial showed use of extended release methylphenidate in ODD comorbid with ADHD and with no ADHD.
- 1 study showed benefit of atomoxetine in ODD , but not replicated in a different study.

Oppositional defiant disorder…

- Several studies of typical and atypical antipsychotics used as adjuncts for treatment of aggression in mental retardation and pervasive developmental disorders.
- AACAP recommends multimodal approach of individual and family psychosocial interventions, parent training interventions.

Oppositional defiant disorder

- Pharmacotherapy used to treat specific ODD symptoms or comorbid conditions ie mood disorder or ADHD, which may improve ODD symtoms.

Tics and Tourette's syndrome.

- Tics occur in 5-20% of children.
- Tourette's syndrome (persistent motor and vocal tics) occurs in 1% of children.
- Most tic disorders are transient, abate with age and don't adversely affect functioning.
- Tics also wax and wane , increase in stress, inactivity and fatigue.
- Tics are 2-3 times more common in boys, than girls.

Tics and Tourettes's Syndrome…

- Mostly, OCD, ADHD, depression, anxiety and behavioural problems are more prevalent.
- Need to treat comorbid disorders, before assessing level of disability caused by tics.
- Most tics do not require pharmacological treatments.
- Education for the child, family and schools are important.
- RCT of Behavioural interventions showed effect size of 0.68, similar to medications for tics.
- Habit reversal and exposure and response prevention are treatments of choice.

Tics and Tourette's disorder.

- FDA approved is Pimozide for managing tics.
- Controlled clinical trials approve of :
- Clonidine 3-5 mg/kg.
- Haloperidol
- Risperidone
- Recent studies show Aripiprazole
- Small and open studies suggest Olanzapine, quitepine.
- Also Sulpiride and Ziprasidone
- No effect for clozapine.
- Most authors recommend second generation APDS.

Tics and Tourette's disorder.

- Botulinum toxin used to treat painful focal motor tics, est affecting neck muscles.
- In subgroup of children with tics/and or OCD with streptococcal infection ie PANDAS, immunomodulatory therapy needed.
- Consensus that tics/OCD treated in usual way.
- A short course of antibiotics for any child presenting with acute onset tics and /or OCD.

Disruptive mood dysregulation disorder

- Symptomatic intervention
- Etiology not well understood
- If similar to bipolar disorder, treat with SGAs and Mood Stabilizers.
- If similar to depression, and anxiety, treat with SSRIs.
- If comorbid with ADHD, to give stimulants.
- Scant studies so far.
- Psychosocial interventions and CBT.

Early onset Bipolar Disorder

- Most well studied are atypicals and mood stabilizers.
- 8 RCTs shown efficacy of atypicals for ages 10-17 years, in both mixed states and bipolar disorder. ie. Olanzapine, quetiapine, risperidone,aripiprazole, ziprasidone.
- In comparative studies, quetiapine and risperidone found more efficacious than valproate, in reducing manic symptoms.

Early onset Bipolar Disorder.

- Lithium efficacious in aggressive mania in adolescents.
- Open trial of Lamotrigine in bipolar depression, supports its use in youth.
- Mood stabilizers overall less effective in BPD in children and adolescents.
- Current evidence suggests faster and more robust response with atypicals, though addition of another drug required when there is partial recovery.

Depressive disorders.

- Fluoxetine and escitalopram have FDA approval in adolescents.
- Sertraline 50- 200mg has been shown to provide efficacy in 2 big trials
- Starting doses of SSRIs lower in children as compared to adolescents.
- Venlafaxine effective in TORDIA study, but 2nd line treatment
- TCAs not recommended
- Overall S/E of behavioural activation with SSRIs.
- In 2004, FDA issued 'blackbox' warning with SSRIs.
- Several reviews since, concluded that there is no increased risk for suicide or serious suicide attempts after starting SSRIs.

Enuresis

- Toilet training review.
- Record keeping, star chart.
- Restricting fluids at night.
- alarm therapy triggered by wet underwear.
- TCAs
- Desmopressin nasal spray. (effect of 10- 90%)
- Antidiuretic, reducing urine at night.
- a/e headache, nasal congestion,epistaxis, stomachache.
- Reboxetine 4-8 mg.

Preschoolers.

- Preschool psychopharmacology working group released recommendations recently.
- Limited evidence base
- Psychosocial interventions always precede pharmacological management.

Preschoolers ADHD

- As per PATS, several small trials, methylphenidate is recommended as first-line treatment in ADHD in preschoolers.

Preschoolers disruptive behavioural disorders

- Risperidone as first line in disruptive behaviours and severe aggression, without ADHD.

Preschoolers major depressive disorder

- 1st line treatment is Fluoxetine

Preschoolers Bipolar disorder

- Most data on risperidone.
- Good efficacy and tolerability.

Preschoolers anxiety disorders

- Fluoxetine first choice for anxiety disorders.
- For OCD, fluoxetine , fluvoxamine and sertraline equally effective.
- For PTSD ,medications not recommended by the working group.

Preschoolers PDD.

- Risperidone approve by FDA for children as young as 5 yrs with aggression and irritability

Preschoolers primary sleep disorders.

- Only if sleep disturbance sufficiently compromises wellbeing and daytime functioning of the child, melatonin 1-3mg considered.

Thank you!