Quiz

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MISSING LINK

Question 1

- Name a SSRI antidepressant that has zero-order (non-linear) kinetics?

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- Paroxetine
  - Zero-order or non-linear kinetics prevail when metabolising or eliminating mechanisms are exceeded or saturated. This results in a fixed amount of drug being eliminated per unit of time, regardless of plasma level.
  - Clinical relevance:
    - Relationship between dose changes and subsequent plasma levels are much less predictable

Question 2

- Products of Phase I hepatic metabolism (hydroxylation, reduction, hydrolysis) are usually less active and toxic than the parent compound
- Name an exception to the above statement

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Name an exception to the above statement

- Fluoxetine --- norfluoxetine
- Imipramine ---desipramine
  - Clinical relevance:
    - Single daily dosing
  - Norfluoxetine has an elimination half life of 7-14 days. Thus SSRI discontinuation syndrome does not occur as there is a gradual “auto-taper” even when the drug is stopped abruptly. For the same reason, the drug should be increased slowly (weekly or 2 weekly intervals) to avoid overshooting the optimal dose

Question 3

- What is the half life of Fluvoxamine?

What is the half life of Fluvoxamine?

- Parent drug has 9-28 hour half life
  - Clinical relevance:
    - Due to short half life twice daily dosing may be required. The drug also needs to be tapered to avoid SSRI Discontinuation Syndrome.
  - Many patients tolerate 50% dose reduction for 3-7 days followed by another 50% dose reduction for another 3-7 days before discontinuation
  - If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly or switch to a drug with a long half life
  - Approved for use in pediatric OCD
  - Potent inhibitor of CYP 450 3A4, 1A2, 2C9, 2C19
  - Important when co-administering Clozapine, Carbamazepine, HMG CoA reductase inhibitors, Pimozide and Thioridazine

Question 4

- Reasons why twice daily dosing is preferred with Clozapine?

Reasons why twice daily dosing is preferred with Clozapine?

- Plasma half life is 5-16 hours
  - Dosing once a day could lead to adverse effects like seizures at peak concentrations
  - Drug dosing and frequency should be tailored to maximise the probability of drug efficacy and to minimise drug toxicity
  - Other dosing tips: Doses above 550 mg/day may require concomitant anticonvulsant medication to reduce risk of seizures

Question 5

- What is the risk of benign and serious rash with Lamotrigine?

What is the risk of benign and serious rash with Lamotrigine?

Benign rash	Serious rash
~ 10%	<1%
Peaks within days, settles in 10-14 days.	
The rash is spotty non-confluent, non tender	Confluent rash, widespread, purpuric or tender; involvement of neck or upper trunk or eyes, lips, mouth
No systemic features	Associated with fever, malaise, pharyngitis, anorexia or lymphadenopathy
Lab tests are normal	Abnormal CBC, RFT, LFT
Reduce dose, warn patient to stop drug if rash worsens, prescribe anti-histaminic and/or topical corticosteroid, MONITOR CLOSELY	Stop Lamotrigine and Valproate (if given). Patient requires hospitalisation and close monitoring
Can be re-challenged with very low titration (5-12 mg/kg/day)	Risk of rash greater in children less than 12 years, those on concomitant valproate therapy, those receiving rapid titration or high dosing

Drug interactions

What is the risk of benign and serious rash with Lamotrigine?

- Valproate increases the plasma levels and half life of lamotrigine
  - Enzyme inducing anti-epileptic drugs (eg. CBZ, Phenytoin, phenobarbital) may increase clearance of lamotrigine and lower its plasma levels
  - OCP may decrease plasma levels of lamotrigine
  - No interactions with Lithium, OxCBZ, atypical antipsychotics or antidepressants
  - Renally excreted
  - Inhibits dihydrofolate reductase and may reduce folate concentrations

Question 6

- What is average plasma steady state?
  - Equilibrium between amount of drug absorbed and eliminated resulting in no net change in plasma concentration over time
  - Equilibrium between amount of drug metabolised and eliminated
  - Equilibrium between amount of drug ingested and eliminated
  - Equilibrium between amount of drug distributed and eliminated

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- Average plasma steady state concentration (Css) is reached when there is an equilibrium between the amount of drug ingested and the amount of drug eliminated resulting in no net change in plasma concentration over time and it is attained after 4-5 half lives

- **Clinical relevance:**
  - Plasma half lives are useful to determine dosing intervals, for therapeutic drug monitoring

Question 7

- Children under 10 years may require …..
  - Larger
  - Smaller
  - Same
  - Not related to age/weight

- Children require larger weight-adjusted doses
- Reasons for the above
  - Weight- adjusted doses of most hepatically metabolised medications are larger than in adults in order to achieve comparable blood levels and therapeutic effects
  - Greater liver to body mass ratio
  - Systemic clearance of nonspecific CYP substrate (antipyrine) is higher in children when compared to adults
  - More efficient CYP system in children
  - Newer anti-convulsants (eg. Levetiracetam, topiramate, lamotrigine) and lithium that are primarily handled by the kidney may also require higher weight-adjusted dosing in pre-pubertal children.
  - Reasons include increased glomerular filtration, changes in tubular reabsorption and increased body water in children is responsible for greater clearance and shorter elimination half lives resulting in the need for larger weight-adjusted doses.

Differences between children and adults

Parameters	Children	Adults
Rate of absorption	Faster	Slow
Peak levels	Early	Late
Hepatic enzymes	More active	Less active
Metabolism	High	Low
Age, weight, sex, disease-state, distribution, protein binding, Vol. Of distribution, body fat	Variable	Variable

Question 8

- Give 2 reasons for therapeutic drug monitoring?

Give 2 reasons for therapeutic drug monitoring?

- Unusual metabolism
- Uncover non-adherence
- Demonstrate increased or decreased concentration with the addition of other drugs (drug interaction)
- Confirm toxicity

Question 9

- In the TADS (Treatment for Adolescents with Depression Study), the overall outcomes (both scalar and categorical) were as follows:
  - FLX > FLX+CBT> CBT>PP
  - FLX+CBT > FLX > CBT > PP
  - FLX +CBT > FLX > CBT=PP
  - FLX+CBT >= FLX > CBT =PP

In the TADS (Treatment for Adolescents with Depression Study), the overall outcomes (both scalar and categorical) were as follows:

- FLX +CBT > FLX > CBT=PP
  - FLX + CBT and FLX alone proved superior to placebo whereas CBT alone did not. FLX + CBT was superior to CBT alone, but not to FLX alone, whereas fluoxetine alone proved superior to CBT alone.
  - The combination produced the greatest improvement in clinical symptoms of MDD.
  - Suicidality: Decreased substantially with treatment
  - Improvement in suicidality was greatest for patients receiving FLX with CBT and least for FLX alone. While fluoxetine did not appear to increase suicidal ideation, harm-related adverse events may occur more frequently in fluoxetine-treated patients and CBT may protect against these events
  - Recent research suggests that the movement from ideation to attempt is facilitated by stressful psychosocial events, substance abuse, agitation, irritability, or disinhibition.
  - TADS findings are consistent with work suggesting that CBT has a specific beneficial effect on suicidal ideation and, importantly, that CBT combined with fluoxetine may confer a protective effect not only against suicidal ideation, but also on harm-related behaviours. (March et al, 2004)

SSRI and suicidality

- FDA – mandated black box warning
- With the use of SSRI for depression the suicide rate in the US fell (7.3/100,000) and climbed up (18/100,000) after the FDA warning
- Increase in new onset suicidal ideation between SSRI and placebo was 4% and 2 %, for a risk ratio of 1.95 (95% CI)
- All reported events refer to suicidal ideation, rather than suicidal acts or completed suicides (Hammad TA, 2006; Hamilton B.E, 2005)
- AACAP guidelines calls for intensive monitoring especially during the early phases of treatment. Weekly in the first 4 weeks, every other week for the next month and monthly thereafter

Question 10

- In the Tourette Syndrome Study Group, children with ADHD and chronic tics were randomly assigned to MPH alone, Clonidine alone, MPH + Clonidine and Pill placebo for 16 weeks.
- Do you think the tics worsened in the children on MPH?

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Do you think the tics worsened in the children on MPH?

- Worsening of tics no higher in the MPH group than in the others
  - Tic severity lessened across all treatment groups in this order (Clon + MPH < Clon alone < MPH alone)
  - Combination treatment had the greatest benefit for ADHD
  - If in individual cases tics are worsened addition of alpha agonists or switching to Atomoxetine can be done
  - Children with TS and ADHD are at a greater risk for a variety of untoward outcomes
  - Was a controversial combination in v/o sudden death. No evidence for the same. Needs to be monitored cautiously however.
  - Always taper Clonidine (Tourette Syndrome Study Group, 2002)

Question 11

In the Treatment of SSRI Resistant Depression In Adolescents (TORDIA) Study, the four treatment arms were:

- Switching to a second, different SSRI (paroxetine, citalopram, or FLX, 20–40 mg)
- Switching to a different SSRI plus CBT
- Switching to venlafaxine (150–225 mg) and
- Switching to venlafaxine plus CBT

Which arm showed more improvement?

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Which arm showed more improvement?

- Adolescents who did not respond to an initial trial of an SSRI, the switch to another antidepressant along with CBT resulted in a higher rate of response than another antidepressant alone
  - Variables predicting better treatment response: less severe depression, less family conflict, and no self-injurious behaviour (non-suicidal)
  - Predictors of poor response: chronic depression, clinically significant suicidal ideation
  - Moderators: More comorbid disorders (particularly ADHD and anxiety disorders), no abuse history, and less helplessness

What have we learnt from TORDIA?

- Median time to a suicidal event was 3 weeks and non-suicidal self injury was 2 weeks.
- Suicidal events were predicted by baseline suicidal ideation, family conflict, and drug and alcohol use.
- Compared with the SSRIs, venlafaxine had a higher rate of self-harm (suicidal & non-suicidal self-injury) in individuals with a history of suicidal ideation.
- Adjunctive use of benzodiazepines also increased the rate of suicidal and non-suicidal self injury
- Early intervention in non-responders is important
- Combination treatment better than pharmacotherapy alone (Brent, D et al 2008)

Question 12

- The Treatment of Early Age Mania (TEAM) Study is a RCT which compares the acute effects of Lithium, Divalproex and Risperidone for 8 weeks in 279 medication naïve subjects with a DSM-IV diagnosis of BPAD in mania or mixed episodes.
- Which drug had the best response rate in the study?
  - Risperidone
  - Lithium
  - Valproate

What can we learn from TEAM?

- Which drug had the best response rate in the study?
  - Risperidone
  - Lithium
  - Valproate
- Response rate: Risperidone (68.5%), Lithium (35.6%) and Valproate (24%)
- Study site was a major source of variability in clinical outcome
- Drop out rate was lower in sites with greater response rate
- Significant amount of site variability
- Long duration of episodes 4.9+/-2.9 years

What can we learn from TEAM?

- Severity of ADHD predicted treatment outcome regardless of medication assignment and the presence of ADHD was a treatment moderator
- ADHD severity predicted a worse outcome even after adjusting for site, medication group and mania severity at baseline
- Children with ADHD responded better to risperidone than to Lithium
- Caveat: large percentage had ADHD to meaningfully compare the two groups and site variability played a major role
- Patients were allowed to continue their stimulant medication
- TEAM focused on treatment of acute mania, no evidence for maintenance (Vitiello et al 2012)

Factors other than specific treatment have a powerful influence on outcome

Medication is part of a comprehensive, integrated treatment plan

Question 13

- 9 year old boy diagnosed with OCD was on 60 mg of Fluoxetine. Developed tics- both vocal and motor and was diagnosed to have Tourette Syndrome. He was put on Risperidone 3 mg/day.
- Developed dystonia – both cervical and oculogyric crisis
- What should you do?
- Acute treatment and maintenance
- What are the precipitating factors for dystonia in this child?

- Check for laryngeal spasms as airway can get compromised.
- Dystonic reactions – extremely frightening and uncomfortable for the child and family.
- Reassure the child and family
- Intramuscular injection of Diphenhydramine (25-50mg) for rapid relief
- Maintenance (Oral): Diphenhydramine 25-50 mg/day or Trihexyphenydyl 2-6 mg/day.
- Reduce the dose of the antipsychotic – Risperidone
- Probable causes – Young boy, rapid escalation of the anti-psychotic dose and co-administration which is a potent inhibitor of CYP 450 2D6

Question 14

- 14 year old girl was diagnosed to have treatment resistant OCD and depression. She failed trials of Fluoxetine (upto 80 mg/day), Sertraline (upto 200mg/day) for adequate duration. She showed partial response to Fluvoxamine.
- She was thus put on Fluvoxamine 200 mg and Clomipramine upto 100 mg/day
- What is the pharmacological rationale for the FLU + CMI treatment option?
- What are the risks with this combination?

Clomipramine

- CMI is a potent serotonin reuptake blocker, at a steady rate is metabolised to its active metabolite desmethyl-clomipramine (de-CMI), a potent noradrenergic reuptake blocker
- In the steady state, plasma drug activity is generally more noradrenergic (with higher de-CMI levels) than serotonergic (lower parent CMI levels)
- Addition of Fluvoxamine (inhibitor of CYP 1A2) blocks this conversion, and results in higher CMI levels than de-CMI levels
- Thus, in treatment resistant OCD, this combination enhances the serotonergic activity of the two drugs

Clomipramine (Contd.)

- SE of CMI: Sedation, dry mouth, constipation, blurred vision, dizziness, increased appetite, fatigue.
- Dangerous side effects: paralytic ileus, hyperthermia, lowered seizure threshold, orthostatic hypertension, sudden death, arrhythymias,
- Risks with the combination: Serotonin syndrome, switch to mania, suicidal ideation/attempt. Caution when using CMI with potent inhibitors of CYP 2D6 and CYP 1A2
- Monitor Wt, BMI, ECG, LFT for CMI

Question 15

- 6 year old boy was diagnosed to have ADHD and put on Methylphenidate 10 mg (IR). The complaints from school had decreased but mother did not perceive any improvement in symptoms. She said he was very hyperactive and she could not manage him at home.
- What is the reason for this behaviour?
- Is MPH working?
- What else should be done?

Rebound Phenomenon

- It is called rebound hyperactivity or rebound phenomenon
- MPH has a very short half life. Clinical action for 2-4 hours. Thus it may be useful to give Methylphenidate SR 10 mg in the morning to cover his school day and 5 mg of the IR preparation as soon as he comes home after school to prevent rebound phenomena.
- Instead of Methylphenidate, Clonidine can also be used to counter hyperactivity
- Other measures including attention enhancing tasks, parent behaviour modification training should go hand in hand with medication for optimal clinical outcome
- Monitor – baseline and monthly rating scales both for the teacher and the parent can be very useful

Question 16

- 9 year old boy, family history of BPAD in father, diagnosed to have ADHD from 6 years of age presented with h/o irritability, temper tantrums that go on for hours, aggression towards people at home for the past year and 2 episodes of significant aggression in school in the past month after which school has asked family to seek help.
- What is your diagnosis?
- Will you continue to treat ADHD?

Mood Disorder

- Hypomania/mania
- Need more information
- Mood diary
- ABC of aggression/temper tantrums
- Irritable mood is the usual type of pediatric mania. Unremitting symptoms lacking discrete episodes is common in pediatric mania
- Necessary to continue to treat ADHD after stabilisation of mood
- Presence of ADHD in children and teens with BPAD maybe a factor that leads to diminished response to Lithium and Valproate

Question 17

- What class of drug does Bupropion belong to?
- Name one serious/dangerous of Bupropion?

Question 18

- Two uses of Bupropion
- Two conditions where Bupropion should not be used

Bupropion

- Bupropion is a Norepinephrine Dopamine Reuptake Inhibitor
- Life threatening SE: Seizures, Hypomania/mania and Suicidal ideation
- Uses: MDD especially retarded depression, atypical depression, Bipolar depression, Patients concerned with sexual dysfunction, patients concerned with weight gain, ADHD, Smoking cessation
- CI: In any patient with h/o seizures, head injury, CNS tumour, Eating disorders,

Question 19

- Give the 3 possible mechanisms of action of Lithium?

Question 20

- What kind of renal impairment does lithium cause?
- How does Lithium cause Polyuria?
- What should you do?

- **MOA:** (possible ways)Alters sodium transport across cell membranes in nerve and muscle cells
- May alter intracellular signaling through actions on 2nd messenger systems (inhibition of phosphatidylinositol and Protein kinase C signaling pathways)
- Enhancement of serotonergic transmission
- Increases cytoprotective proteins, activates signaling cascade utilised by endogenous GF, possibly increases neurogenesis and enhancing trophic actions that maintain synapses

- Renal impairment: Chronic interstitial nephritis
- Lithium inhibits renal tubular response to ADH and therefore decreases the kidney's ability to concentrate urine
- Decrease total dose, switch to a long acting preparation, entire dose at night, addition of low dose of a pottasium sparing diuretic such as amiloride. If they develop nephrogenic DI need to discontinue Lithium

Bonus questions

- Name two drugs with the highest association with suicidal ideation and have been advised against routine use in pediatric psychopharmacology

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- Name two drugs with the highest association with suicidal ideation and have been advised against routine use in pediatric psychopharmacology
  - Venlafaxine
  - Paroxetine

Thank You