Mental Health and MI

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Plan

- General considerations for people with serious mental illness (SMI)
  - Reduced life expectancy
  - Suicide
- Considerations for specific medicines
  - CLOZAPINE
  - Lithium
  - Long-acting antipsychotics (LAIs)
- Other issues in an acute setting
  - Serotonin syndrome
  - Nil by mouth
  - Suicide disclosure

General considerations for people with SMI

- Life expectancy reduced by ~15-20 years
- Mortality rates compared with general population:
  - Schizophrenia – 2 to 2.5 x higher
  - Bipolar disorder – 1.3 to 2 x higher
  - Moderate to severe depression – 1.8 x higher
- Likely to receive lower quality health and social care than the general population
  - central cause – stigma and discrimination (69%)
  - MH symptoms act as barrier to seeking or following advice

General considerations for people with SMI

- Majority of deaths are due to chronic physical conditions
  - Cardiovascular = leading cause
    - CHD, atherosclerosis, hypertension, stroke
  - Also higher than expected rates of:
    - Respiratory and infectious diseases
    - Type II diabetes
- Lifestyle
  - Higher rates of smoking (schizophrenia = 3x) – self medication?
  - Lack of exercise
  - Poorer socioeconomic status
- Suicide
  - Schizophrenia = ~12x

Clozapine – a potted history

- Early 1950s:
  - Accidental use of chlorpromazine in France – became 1st antipsychotic
  - Imipramine structurally similar – no antipsychotic activity
- Wander laboratories – late 1950s: developed clozapine
- Structure indicated potential for antidepressant activity
- No antipsychotic activity in animal screening
- Profound effects – humans
- No EPSEs → Wander reluctant to market as "all antipsychotics cause EPSEs and must be part of the therapeutic action….?"

CLOZAPINE – a potted history

- 1966 – 100 subjects
- Wander acquired by Sandoz (who marketed thioridazine)
- 1969 – + patient exposures = 2200
- 1971 first double blind trial reported (n=64, vs levomeprazine, mania & schizophrenia, no EPS)
- 1970s series of small studies
- Superiority over chlorpromazine detected
- No EPSEs

Neutropenia & agranulocytosis….

- Known rare risk of phenothiazines
- Clozapine introduced in Finland: 1975
- Rise in reports noted c.f. previous year: 18 (9 deaths)– all on clozapine
- Use suspended worldwide
- Two major controlled trials published in 1990 supported re-registration with mandatory FBC monitoring
- Recent effectiveness studies confirm superiority over other antipsychotics in TRS
- Suicide prevention; TD

FBC monitoring

- Weekly for 18 weeks
- Fortnightly from week 18 to 52
- Monthly thereafter
- Continue monitoring 4 weeks after discontinuing.

Red	Amber	Green
WBC <3.0 x 10^9/L or Neutrophils <1.5 x 10^9/L or platelets <50 x 10^9/L	WBC 3.0-3.5 x 10^9/L or Neutrophils 1.5 – 2.0 x 10^9/L	WBC > 3.5 x 10^9/L and Neutrophils >2.0 x 10^9/L and no decrease of >10% or repeatedly decreasing values in the previous test(s)

CLOZAPINE – why does MI get contacted?

- **Supply** = main reason an acute trust MI service/pharmacy might call MH MI/pharmacy
  - However we will always ask about reason for the admission

- **Other reasons we might receive calls from acute Trusts:**
  - Treatment breaks
  - NMB advice
  - Advice about plasma level testing
  - Compatibility with oncology treatments
  - Other interactions and adverse effects

But, ward pharmacists should also consider……

- Smoking cessation – significant interaction…..(CYP1A2)
- Most seizurogenic AP (plasma level related)
- Strongly anticholinergic – care with pharmacodynamic interactions
  - Confusingly causes hypersalivation…..
  - Constipation = very common
- High risk of metabolic adverse effects
- Cardiovascular risks
  - Tachycardia
  - Hyper- / hypo- tension
  - Myocarditis (fatality rate high)

CLOZAPINE and the GI Tract

- Affects whole GIT – from swallowing difficulties to rectal bleeding
- Clozapine – minimal D2 antagonism but…
- Potent peripheral anticholinergic effects:
  - Delay colonic transit
  - Relax intestinal smooth muscle
- Antagonism at serotonin receptors:
  - Compounds the inhibiting effects on smooth muscle contraction
- Constipation = very common, up to 60%, usually benign
- Compounded by poor lifestyle – diet, fluid, exercise etc.

Under-recognised….

- Unrecognised CIGH → rare but potentially fatal consequences
- Many reports of death associated with:
  - Aspiration of vomit secondary to bowel obstruction
  - Toxic megacolon
  - Necrotising colitis
  - Colonic perforation
  - Abdominal compartment syndrome
  - Bowel infarction
- Other life-threatening illness where hypomotility found to be a likely cause:
  - Sepsis, organ failure, pneumonia, cardiac abnormalities
- Prevalence of life-threatening CIGH = 3 per 1000

Under-recognised….

- *** CIGH is significantly more of a risk than blood dyscrasias***

Up to 2013:

- 5061 reports of GI ADRs – 82 = fatal
- 5 blood disorder fatalities during same time frame

- Risk factors include
  - High dose
  - Stopping smoking
  - Age
  - Co-prescribing with other constipating drugs*

Drug Safety Update volume 11, issue 3; October 2017: 4.

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Clozapine: reminder of potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus

If constipation occurs during treatment with clozapine (Clozaril, Denzapine, Zaponex), it is vital that it is recognised and actively treated.

Published 26 October 2017
From: Medicines and Healthcare products Regulatory Agency

Other uncommon /unusual ADRs of clozapine

- Colitis _____ a few reports, causal link not clear, → refer
- Delirium _____ rarely seen if slowly titrated & plasma levels monitored
- Eosinophilia _____ fairly common
- Heat stroke _____ may interfere with thermoregulation (& other APs)
- Hepatic failure _____ rare (benign changes common)
- Interstitial nephritis _____ handful of reports
- Pancreatitis _____ rare, sometimes associated with eosinophilia
- Pneumonia _____ aspiration of saliva (v rare); infection rate higher – important to note that respiratory infections = raised clozapine levels
- Thromboembolism _____ known risk with APs – possibly highest with clozapine. Threshold for prophylactic antithrombotics (immobility, surgery etc) should be low

LITHIUM

- Toxicity
- Nephrogenic diabetes insipidus
- Hypothyroidism (but also rarely hyperthyroidism, and thyroiditis)
- Manic relapse – high risk with intermittent Tx or abrupt stop

- What is the indication?
  - Acute treatment of mania
  - Relapse prevention in bipolar disorder
  - Augmentation in unipolar depression
  - Boosting white cells in clozapine-induced neutropenia….

Long-acting antipsychotic injections

- Risperidone LAI – unusual release kinetics
- Paliperidone LAI – initial loading regimen, available as monthly and 3-monthly injections
- Aripiprazole LAI – one treatment/maintenance dose
- Olanzapine LAI – requires 3 hours of post injection observation

A few considerations….

- Monthly not 4-weekly (except RLAI = fortnightly)
- Route of administration – deltoid / gluteal
- Often lee-way built in to the product licence for missed doses
- Doesn't necessarily indicate poor compliance
- Persistence after discontinuation

Serotonin syndrome

- Predictable effect of drug induced excess serotonin agonism
- Degree of elevation determines severity
- Dose and potency for 5HT agonism influence toxicity
- Triad of neuroexcitatory features
  - Altered mental status (agitation, excitement, confusion)
  - Neuromuscular hyperactivity (tremor, clonus, myoclonus, hyperreflexia)
  - Autonomic hyperactivity (diaphoresis, fever, mydriasis, tachycardia, tachypnoea
- Spectrum of severity
  - Mild eg: SSRI + lithium
  - Moderate eg: SSRI overdose
  - Severe eg: MAOI + SSRI

Serotonin syndrome

- Be aware if other serotonergic medicines are commenced e.g. for surgery
- Examples:

Valproate	Ondansetron	Triptans
Lithium	Granisetron	Quetiapine
Fentanyl	Metoclopramide	Aripiprazole
Pethidine	Tramadol	etc….

- Useful section in Maudsley Guideline about psychotropic drugs and surgery (table 13.4, p781-786)
  - anaesthetic requirements may be different; drug interactions –alpha blockade = additive hypotension; QT interval prolongation, arrhythmia risk; increased bleeding risk

Nil by mouth

- Consider:
  - Time frame for NBM
  - Half-life of medication
  - Alternative routes of administration?
  - Risk of relapse?
  - Risk of discontinuation symptoms

Suicide disclosure

- It is ok to ask the question
  - listen, be supportive, get help on their behalf
- Other considerations while in hospital:
  - Is there a risk of stock-piling?
  - Obtain a mental health review – does medication need changing, starting etc..
- Mental Health First Aid training

Reference sources

- Maudsley Prescribing Guidelines in Psychiatry 13th edition
- Psychotropic Drug Directory 2018 (Bazire, S.)
- Life threatening effects of antipsychotic drugs (Manu, P., Flanagan R.J., & Ronaldson, K.J., Elsevier 2016)
- Clozapine Handbook 2013 (Bleakley, S., & Taylor, D, Lloyd Reinhold Communications)
- Adverse syndromes and psychiatric drugs- a clinical guide (Haddad P, Dursun S, & Deakin B)
- BAP guidelines (https://www.bap.org.uk/guidelines)
- Issues acute Trust pharmacists should consider when dealing with patients with a mental health diagnosis: (https://www.sps.nhs.uk/wp-content/uploads/2018/03/Acute-trust-medication-issues-on-admitted-mental-health-patients-Sussex-Partnership-NHS-Foundation-Trust-Jan-18.pdf)
- Your local mental health MI service…. ☺