Slide 4

Criteria: Unsuccessful trials of two different antipsychotics at a sufficient dose for a sufficient period. Needs to be treatment resistance not resistance to treatment of course! The meds only work if they can get into someone's system…

Slide 5

Three different types of issue:

Clinician issues – prescribers and healthcare staff alike - lack of knowledge or experience regarding the management of side effects are the most common clinician-related barriers. I also find lack of appreciation of positive effects especially the effect staff members' cognitive biases can have on their willingness to use it once they've worked with someone who has had a significant adverse event, or in secure environments where the folks that get well move on and are no longer on the radar so the folks that the nurses generally work with are the ones that don't respond… Or with patients that have a short inpatient stay and staff see the initiation adverse effects but don't work with the patient long enough to see them get properly well. Clinicians influence one another too. I've been around the system long enough to see senior medics influence the juniors in their subsequent practice via their general attitude to clozapine – especially if they have a risk averse approach or feel if someone has an adverse event that they'll end up being litigated against/in coroner's court. Other professionals e.g. social workers and psychologists can be opinionated but not necessarily adequately informed – and likewise they can be great advocates and provide excellent supportive challenge! – it's about operating as a team 😊.

Patient issues – significantly influenced by the clinician issues! Make sure you surface and bust myths, work alongside what the person wants and do stuff with rather than to them!

Systems issues – difficult to tackle but do need surfacing and working through.

Note I use the word perception a lot… Also, that very little of this is actually about the drug itself…

Slide 7

When clozapine first came onto the market, it caused some fatal blood dyscrasias – and was rightly withdrawn. In the time that it was available though, it was noticed that it was more effective than other antipsychotics, so the case was made to relaunch it but with FBC monitoring requirements as part of licensing. Each manufacturer has their own monitoring system (makes brand swaps interesting! – and not something that can be done at the drop of a hat). These requirements made clozapine accessible again and have successfully decreased both the occurrence of agranulocytosis, and the risk of an agranulocytosis being fatal. FBC results are grouped into green, amber and red as a means of highlighting what can and should occur in response. Green is go, amber is be cautious and red is stop! FBC frequency is informed by risk of blood dyscrasias – risk is higher at the start of treatment, so FBCs need to be done more frequently. Think about that around surgery, for instance, and also as clozapine interacts with anaesthesia – use manufacturer guidance.

Slide 8

Questions:
What is the diagnosis?
Is Danny a clozapine candidate?

The diagnosis is treatment-resistant schizophrenia – incomplete response to two antipsychotics at a sufficient dose for a sufficient time (generally at least four weeks). Crucially, adherence has been assured (by the use of serum olanzapine levels, followed by use of long-acting injectable paliperidone) – so Danny can be said to be treatment-resistant rather than resistant to treatment. There are also no overt confounders/differential diagnoses e.g. substance misuse. Danny is absolutely a clozapine candidate! - according to both any national or international guidance you choose to consult, and the summary of product characteristics/product license – he has failed to respond to two antipsychotics at a sufficient dose for a sufficient time.

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You will probably need to cross-titrate the clozapine with the olanzapine to prevent a further mental state deterioration, whilst keeping the time of concurrent antipsychotic use to a minimum, in order to decrease the risk of a blood dyscrasia occurring. Advice is often given that the safest option from a blood dyscrasia perspective is to completely withdraw the first antipsychotic prior to starting the second one. This is true but risks mental state deterioration and can take an extended amount of time (especially for depot or long-acting injectable antipsychotics). The risk of mental state deterioration is higher than the risk of blood dyscrasias, so this advice is generally felt to be impractical.

Clozapine will be started at a low dose and slowly increased – the general aim is to reach 300mg/day over a couple of weeks, so decreasing the olanzapine by 5mg/day twice a week

or 10mg/day once a week given it will take roughly a week to reach steady state will provide a sensible cross-titration. Consideration of half-lives is vital when you're trying to maintain a consistent overall antipsychotic load in someone's system during a cross titration.

Other things to consider will be a) withdrawal effects of the old agent, b) additive side-effects from the combination and c) initiation effects of the new agent. Olanzapine is sedative and anticholinergic, but so is clozapine so cholinergic rebound and a lessening of sedation that could be mistaken for mental state deterioration are unlikely. Both agents are sedating, and anticholinergic plus can cause blood dyscrasias, so the effects of these should be monitored and the cross-titration reviewed if need be. Clozapine causes postural hypotension so a low dose and slow titration will minimise this.

Think about dose timing/splits, forms of medicine to use, ease of prescribing and ease of nurses following the medication charts. If in a community setting you'd also look at e.g. whether an adherence aid may be useful, prescription charges, and availability of support/oversight too.

Physical observations should occur regularly - pulse, BP (consider sitting and standing), and temperature should all be closely monitored. NEWS scores (or similar) should be calculated and any deterioration in physical health should be checked out – myocarditis and NMS (neuroleptic malignant syndrome) are rare but tricky to detect and can be fatal. Neither agent affects prolactin or causes EPSEs (extra-pyramidal side effects), so that shouldn't be an issue. Both agents are associated with constipation, weight gain, glucose dysregulation and lipid abnormalities, so these should continue to be monitored. Clozapine causes hypersalivation, so this needs to be specifically monitored for. And of course mental state needs to be monitored to check the change is a positive one from an efficacy perspective.

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The second level is likely to be a non-trough level as the clozapine is high but the norclozapine (clozapine's active metabolite) remains congruent with the other results. We all love certainty even when it doesn't exist! – so we may rely on numbers irrespective of what the numbers actually mean… So, pharmacy professionals have a massive role to play here, in interpreting the levels and heading off any inappropriate responses.

Clozapine is NOT a narrow therapeutic range drug. If the level is low and the patient is doing well, leave it alone! – but if they're not, push it into the range if you can. If the level is slightly "high" and the patient tolerates it and doesn't do as well on lower levels, leave it alone!

Clozapine levels also generally take some time to report so if you think there's a real issue are you REALLY going to wait a week or so to do anything?

Is a "low" level because it was taken too late? – and the converse for a "high" level?

Levels need to be taken about a week after any dose changes to be at steady state.

If it's a BD dose was the mane dose withheld or not?

Look at the norclozapine as it helps add context.

The evidence is based on BD dosing so it's not totally clear how relevant they are to OD dosing. Try not to get sucked into people's need for surety leading them to make something concrete when it isn't e.g. using equations to allow recalculation or results for different dosing regimens. They're just not robust enough to be making decisions about patient care on, if used in isolation.

Remember levels only really tell you what's been happening over the past few days – and that patients aren't stupid if they know a level is planned.

And DO NOT change the timing of the dose the day before to make it a "trough" level – it won't be. If a patient always has their dose in the early evening, just be zen with the fact that their level will look low.

Think about interactions, and timeframes – if it's to do with CYP450 hepatic enzymes then there's a lead in time to consider and a waning time to consider.

Think about constipation as it decreases levels due to locking clozapine away from being absorbed in a non-motile faecal plug – and then levels spike when constipation resolves and normal churn and peristalsis returns. Levels can also be affected by infection. Bear this in mind if e.g. admitted to a medical setting/started on opiates after surgery etc.

When the result was obtained, Danny should have been checked out for any clinical indications of increased levels e.g. increased drowsiness or hypersalivation, and also any potential ictal activity such as twitching (myoclonic jerks). Clinical presentation should always be the main driver of any response to a clozapine serum level, unless it is very low, or very high.

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Sedation

May wear off, utilise sleep hygiene, give most/all of dose at night/in evening, lower the dose. Is it actually the clozapine? – can the person get out of bed if it's something they want to do rather than a boring ward round?

Drooling

We sometimes get more upset about adverse effects than patients do – is Danny actually bothered by the drooling? Bear in mind though that this can increase the risk for RTIs including aspiration pneumonia. Various physical strategies can be used – putting a towel on the pillow, sucking ice chips or sugar-free sweets, chewing sugar-free gum (remembering of course that some of these strategies may not be accessible in an inpatient unit – chewing gum is generally banned as it can be used to gum up locks or make key impressions). Medication strategies

include hyoscine, pirenzepine, and others. All are equally as effective so choice will depend on side-effects, any relevant co-morbidities and patient choice. Remember the requirements that using licensed medicines in an unlicenced manner, or unlicensed medicines, confer.

Constipation

Conversely, we sometimes get less upset about adverse effects than we should. Constipation needs detecting and dealing with proactively, as if it progresses to toxic megacolon, it can be fatal. The constipation needs to be qualitatively assessed in the context of usual bowel habits, and the laxative chosen accordingly. The Bristol Stool Chart may help assess issues objectively but remember patients (and staff) may find enquiries about bowel habit embarrassing or it may drive the patient's paranoia so the monitoring plan should fit the patient rather than a standard approach being used. Bear in mind patients may be cognitively impaired and so unable to tell you when they last went to the toilet. Also, low-fibre hospital food and poor fluid intake may be significant contributors – remember to think holistically when treating constipation. And if someone reports diarrhoea, please make sure it's not overflow before recommending loperamide…

Postural blood pressure drop and (reflex) tachycardia

Should wear off, slow the titration, strategies for standing up/getting out of bed, may need a beta blocker (e.g. bisoprolol) if tachycardia doesn't wear off after titration has been completed.

Sore throat/generally unwell

Check he's not been to a music gig the night before and by all means recommend symptomatic treatment but please make sure a FBC gets done too. Agranulocytosis - stop the clozapine, manage symptomatically, deal with any additional risks (meds, Covid). If it's a real one, all bets are now off… And several of the scary clozapine adverse effects like myocarditis, toxic megacolon and neuroleptic malignant syndrome present non-specifically with someone becoming increasingly generally physically unwell - so if someone doesn't look or feel right, please do get them medically checked out. Things caught early may be treatable but once they progress, mortality rates are high. Stop the clozapine and manage symptomatically.

Urinary incontinence at night

Elucidate if the person is oversedated (doesn't wake up in time) or this is an urge issue (wakes but can't get to the toilet in time). Minimise the dose/look at dose splits. The former requires dose minimisation/review of dose splits and timing. The latter may be treated using e.g. desmopressin.

Seizures

Myoclonic jerks are often a harbinger of seizures. They are associated with high levels NOT dose – check causes and decrease dose. If someone has a seizure, withhold clozapine for 24 hours, start an antiepileptic drug (e.g. lamotrigine NOT carbamazepine or phenytoin, and maybe valproate), restart at half the dose.

Breathlessness

Think about context and circumstances. Has Danny put weight on with clozapine (it's not deterministic like a lot of folks think!)? Is he too tired to exercise? Is he developing cardiac insufficiency? Does he have a VTE – especially if he's been inactive/post-op? Response will depend on cause.

Smoking

Polyaromatic hydrocarbons in cigarette smoke (not nicotine!!!!) induce liver enzymes and drop clozapine levels – maximal effect at around 8-10 cigarettes a day, so it's not the initial bit of a quit attempt that has the most effect… Important in either direction and can happen within a week. Main thing is to get to know about it so can monitor and tweak clozapine dose accordingly. Bear in mind this interaction will occur in environmentally-imposed scenarios e.g. admission to hospital, and that passive smoking has an effect too.

Treatment break

If > 48 hours need to retitrate dose from scratch as lose tolerance to alpha effects on BP. If > 72 hours may need to look at resurrecting more frequent FBCs. Contact manufacturer for guidance.

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Stay on the clozapine! Tell any health professionals you consult that you are on it. Don't ignore signs and symptoms of infection – contact your clinical team. Tell your clinical team if you start or change smoking habit. Have your blood tests done when you should (explain how he'll know this and how to get them done). Explain how he is to get hold of his meds and who to contact if he has concerns. Any new/ongoing/worsening constipation should be discussed with a health professional immediately. Any signs of symptoms of infection should be checked out with the CMHT/GP. Emphasise the importance of good diet, exercise, and adequate fluid intake. Talk about how to manage alcohol and clozapine sensibly - reissue e.g. Choice and Medication leaflets if needed. Plan your holidays via discussion well in advance with your clinical team (and especially if you're still under compulsory treatment!).

Slide 13

But they can't take it?

- Most adverse effects e.g. seizures - Generally treatable but definitely won't be while the person is unwell…
- Most comorbidities e.g. cancer/chemotherapy - Generally treatable but definitely won't be while the person is unwell… Ensure proactive liaison with manufacturer occurs so monitoring can be individualised.
- Neutropenia - Rechallenge after removing any potential precipitants/contributors.
- Agranulocytosis - If it's a real agranulocytosis then don't go there! Several other things e.g. Covid/infection, other meds (carbamazepine!) can contribute but manufacturer will deregister anyway. Can retrial if it's not a real one but will be unlicensed…

I have to admit I'm not a huge fan of artificially boosting blood counts using GCSF or lithium in order to comply with the semantics of the licensing – neither agent is benign, both need to

be monitored, lithium can be toxic, GCSF needs to be injected, evidence isn't brilliant. Instead I'd prefer to work with a haematologist to individualise the parameters for the patient, and use those…

But they won't take it?
Explore reasons – bust myths. Get the whole team on board with persuasion. Get a patient champion who is taking it involved. Surface and deal with any adverse effect concerns. If it is in the person's best interests, consider short-acting IM if oral refused.

But it's not working?
Wait – it takes time… Optimise levels. Augment – target symptoms. Common augmentation agents are amisulpride, or mood stabilisers. But DO NOT be artificially inflating levels using fluvoxamine/cimetidine – not licensed, not predictable, would need consent (so why not just increase the dose formally??), it's ok until the interacting agent changes etc…