Pharmacology:
- neuroleptics: first line
- benzodiazepine: only ethanol and bento withdrawal.

Generally haloperidol (typical antipsychotic) was the main drug used. With the advent the second generation antipsychotics these have challenged this. There have been two previous cochrane reviews. One discusses nonage specific delirium and other shows equivalence. More recent literature is below.

Boetter, S., Breitbart., 2005. Review Article: Atypical antipsychotics in the management of delirium: A review of the empirical literature. Palliative and Supportive care. 2005, 3: 227-238.

Goes through each drug and positive versus negative: summary of papers in tables
- Respiradone: Benzisoxazol acts on 5HT 2a , DA2, a1 receptor sites
  - +ve: Linear PK and reaches steady state within 24hrs. May be faster onset than haloperidol & lower EPS (but still possible at high doses). Effective in hyperactive and hypoactive subtypes. Average dose 0.5-4mg. 95% of patients recovered from their delirium. As effective as haloperidol
  - -ve: Wooltorton 2002 reported increased CVA risk-so USA put caution out.

- olanzapine: a thienbenzodiazepine- similar to clozapine. A strong 5HT2a, Histamine, muscurinergic M1 receptor and only moderate D2.
  - +ve: rapid onset and significantly fewer adverse EPS compared to haloperidol. Significant sedation. Mean dose 4.6mg. Max 8.8mg. Suggest starting 2.5mg and titrate upwards with limitation of sedation.
  - -ve: Those 70yo older had less improvement (ir 2 patients 80+ worsened with it). Sedation occurred in 30%. Due to its strong antihistaminergic activities more sedating. In the elderly with hypoactive delirium it isn't very effective.

  - Quetipapine: dibenzothiazepine structurally similar to clozapine and olanzapine. High a1 adrenergic receptor with moderate 5ht2a and histamine receptor. Low affinity to D2
    - +ve: 25mg BID. Maximum dose 150mg. No EPS. Its antihisterminergic activity may help with sleep-wake cycle.
    - -ve: Some sedation which may limit it.

Limits to studies:
- limited number of subjects
- Most use DRS and MDAS measures of delirium
- Lack of differentiation between subtypes of delirium.
- Respiradone & olanzapine provided studies with largest numbers.

Boettger, S., Jenewein, J., Breitbart. Haloperidol, respiradone, olanzapine and aripiprazole in the management of delirium: A comparison of efficacy, safety, and side effects. Pallattive and Supportive Care. 2015 13:1079-1085.

Aim to compare the efficacy and ASE of typical vs atypical (respiradone, olanzapine, aripiprazole)
Result: equally effective int eh management of delirium however they differed in terms of ASE. EPS were more frequently recorded with haloperidol and sedation more frequent with olanzapine.
- MDAS score (>10= delirium). Memorial Deirium Assessment Scale
- haloperidol 5.5mg, risperidone 1.3mg, olanzapine 7.1mg (big dose)
- table 1: etiology of delirium: opioids, corticosteroids, hypoxia, infection, CS infection, dehydration
- ASE:
  - haloperidol: 19% total-all parkinsonism
  - respiradone: 4.8% total-all parkinsonism

- olanzapine: 42.9% total: 28.6% sedation, 14.3% worsening delirium.
- efficacy:
    - haloperidol 76.2% (58.3-87.5%)
    - Respiradone 85.2% (42-84.4%)
    - Olanzapine 61.9% (64.7-82.4%)

Vardy, E., Teodorczuk, A., Yarnall, A. Review of delirium in patients with Parkinsons disease. Journal of Neurology 2015: 262:2401-2410.

PD is suggested t be a risk factor for delirium and delirium negatively impacts upon the motor symptom trajectory.

Of the atypical antipsychotics quetiapine has the least EPS.

Great photo of how inflammation ==> delirium (fig1)

Mediation review: stop the least antiparkinson and most delirium inducing:
anticholinergic –> amantadine –> selegeline –> dopamine agonists –> carbidopa-levodopa.

Mention a Cochrane review on the use of antipsychotics for delirium of haloperidol versus olanzapine but no specific input for PD/geriatrics.

HALOPERIDOL contradicted in PD due to risk of EPS and risk of NMSY
OLANZAPINE: likely effective but unacceptable motor deterioration

" In summary, atypical antipsychotics have less EPS compared to haloperidol which should not be used in the PD or related disorders. Quetiapine appears to have some efficacy and least side effects. However cautious interpretation of the efficacy of quetipaine should be applied to existing studies have been statistically underpowered and in many cases not incorporated with a control group ".

Kishi, T., Hirota, T., Matsunaga, S., Iwata, N. Antipsychotic medication for the treatment of delirium: a systematic review and meta-analysis of randomised controlled trials. Journal of Neurology, Neurosurgery and Psychiatry 2016: 87: 767-774.

Showed that SGAs have a benefit for treatment in regards to efficacy and safety when compared to haloperidol.

PRISMA review diagram. 15 studies

Neither grouped SGA nor individual SGA outperformed haloperidol for day 2-3 endpoints. however there was shorted TTR (time to response) and lower incidence of EPS. Olanzapine was superior to haloperidol in TTR and incidence of dystonia. SGAs were better than haloperidol for DSS endpoints in ICU but not in noED setting.

There was no difference between olanzapine and respiradone on day 3

summary: "Given our results confirming safety of SGAs in comparison to that of haloperidol in the treatment for patients with delirium, we suggest that the clinicians choose SGAs prior to the trial of haloperidol for the treatment of delirium. Owing to the limited number of studies, were unable to explore which SGAs should be used for the treatment of delirium".

Table 2: the results of meta-analyses: SGAs versus haloperidol pg 773.

Alici-Evcimen, Y., Breitbart, W. An update on the use of antipsychotics in the treatment of delirium. Palliative and Supportive Care. 2008: 6:177-182.

The delirium syndrome is thought to be a a common pathway of UNDERACHIEVE cholinergic system. Cytokines could also contribute.

3 forms: hyperactive, hypoactive and mixed type.

haloperidol: Often DOC in the treatment of delirium due to high potency, low sedative effect, few anticholinergic side effects, minimal cardiovascular side effects, no active metabolites and available routes. **_***IV dosing is less likely to produce EPS_**

Olanzapine: Age over 70 and history of deentia, hypoxia, cerebral metastasis and hypoactive delirium were associated with poor response.

Quetipine: sedation was the most common ASE.

Low dose haloperidol was not effective to prevent postoperative delirium 1.5mg/day

Respiradone 0.25-1mg and titrate up to look for EPS, orthostatic hypotension and sedation and higher doses:

Olanzapine started between 2.5-5mg nightly.
Quetipaine 25-50mg and then titrate up to 100-200mg/day.

Nagaraj, G., Burkett, E., Hullick, C., Carpenter, C. Is delirium the medical emergency we know least about? Emergency medicine Australasia 2016: 28: 456-458.

Respiradone is equal to haloperidol but less routes (no IV, but SL, quicklets, PO).
Start either at 0.25mg in a frail patient or 0.5mg if not naive. Maximum q4hr
Olanzapine is comparabale 1.25mg PO/IM or 2.5mg- no further for 6 hrs

Factors:
- what is your use: deescalation vs prophylaxis
- Patient co-morbidities: PD/LBD
- how quickly do you need it to work
- Dose: naive
- route
- type of delirium (3 types hyper/hypo/mixed)

current issues with delirium pharmacology:
- not ED specific
- perioperative and ICU specific more abundant.
  - - most literature is post hip replacement
  - others for ICU/ETT delirium