‘Terminal Agitation’
An Overview…

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EoLC Study Day, London, November, 2019
Jobbing Consultant…

- **Princess Alice Hospice**, Esher, 1995 -
  - Medical Director, Consultant in Palliative Medicine
- University of Surrey, Guildford, 2012 -
  - Visiting Professor

- **Association for Palliative Medicine**
  - ex-Ethics Committee, 2009 – 2019
- **Royal College of Physicians**
  - SCE QWG, Exam Board 2010 - 2016, SSG, 2016 -

- **Publications / teaching**
  - Ethics BMJ, JME, IJPN, CE, NE
  - Ethics MSc University of Surrey, MA St Mary’s University
  - Methadone CSI KCL, PANG, OHPC, ECEPC
J7 to J14 of M25
Care Area ~1,000,000 Population
Management of ‘Terminal Agitation’

To drug, or not to drug... that is the question...?

Benedict Cumberbatch as Hamlet, Skull as Yorick, 2015
• ‘My’ view… not tell what is ‘right’
  – ‘One’ perspective
  – Challenge *conventional* wisdom…
  – Make your own mind up

• Content systematic review, last 5 years, (Aug 2019)
  – Terminal agitation / terminal restlessness (n=108/26)
  – Skip slides with *textbook* answers / lists
  – Slides are yours / get the book, far better…!
A Memorable Patient…
>25 Years Ago

The Wright Flyer, 1903
A “Difficult” Home Visit…

- Visit patient’s home, 1991
  - Final-year GP trainee

- 77-year-old man
  - Carcinoma of colon, multiple liver metastases
  - Terminal… dying, bed bound, no more treatment

- Abdominal pain
  - Distressed… agitated
  - “…needs his morphine increasing”
Memorable As... Daunting

• Colleagues distant
  – Didn’t “do dying" patients

• First contact
  – Bedside vigil
  – Wife & 2 sisters-in-law agitated

• Nothing to offer
  – “Terminally agitated” in pain
  – Increase morphine…?
  – Panic…!
  – Resorted to basics…
Memorable As…
Valuable Lesson

• Two brothers both died Ca Colon
  – Family history missed
  – Increased impact patient / family

• Pain from constipation not tumour
  – Needed laxatives / DN interventions

• Agitation from pain and drugs
  – Morphine making pain worse and sedating – not ‘dying’…?

• “You’re the first doctor to examine my husband”
  – Embarrassed only did it as lacked confidence
  – Embarrassed by approach of colleagues
Memorable As... Valuable Lesson

- Two brothers both died Ca Colon
  - Family history missed

If I had given morphine...

1. Acute increase confusion (proportional toxicity)
2. Agitation worse (as pain worse)
3. Reinforce looks like dying...

Terminal Agitation...!!

- Embarrassed by approach of colleagues
Terminal Agitation
Self-Fulfilling Prophecy

POLITICIANS NEVER DO WHAT MY GROUP WANTS, SO I NEVER VOTE.
Summary: NOT Terminal Agitation

- **Catastrophic** body failure as dies
  - Not discrete diagnosis
  - Significant *distress* common, all stakeholders…
  - Inevitable – must re-frame *expectations*
- **Before final hours** manage as ‘*delirium’*
  - Assessment key; don’t under-estimate *hypoactive delirium*
  - Reversibility; don’t dismiss, reverse or delay, reduce
  - Avoid / remove causes of agitation
  - Good evidence *non-drug interventions*, must do better
  - Weak evidence drugs, net harm, must do less harm
- **In final hours** – manage as ‘*dying*’
  - U-turn family / staff; antipsychotic, benzodiazepine etc…?
Terminal Agitation…

- **Common**
  - 13% – 42% – 88% SPC IPU
  - Increases last weeks / hours of life

- **High levels** distress
  - Patient…
  - Emotive family… **not** promised ‘good death’
  - Guilt HCPs… **not** promised ‘good death’
We Need a Shared Understanding of Terminology…

- ‘the patient in room 18 is *terminally agitated*’
Terminal Agitation is NOT Simple

- **NOT discrete disease**
  - Multiple socio- / pathological conditions

- **NOT discrete presentation**
  - [1] “Agitation” is *ill-defined / misleading* umbrella term
    - Constellation of *signs* > anxiety symptoms
  - [2] “Terminal” dangerously ‘*presumptive*’
    - 10% to 15% of T/C hospice admissions are *discharged*
Terminal Agitation is NOT Simple

• NOT discrete disease

• NOT discrete presentation – [1] “Agitation” is ill-defined / misleading

• Constellation of signs > anxiety symptoms

• [2] “Terminal” dangerously ‘presumptive’

  • 10% to 15% of T/C hospice admissions are discharged

Diagnosis... essential in order to:

• Reverse reversible
• Target palliation
• Explain / prepare patient, family colleagues

A Restless Mind by Gabriela Taylor
Is ‘Terminal Agitation’ Even a Discrete Syndrome…?

• [1] Pattern of commonly observed behaviours:
  – Waning / absent awareness / wakefulness
    • Confusion to coma
  – Involuntary, spontaneous muscle contractions
    • Twitching or jerking
  – Voluntary but appear purposeless movements, mimic control
    • Fidgeting, pacing, fumbling, tossing / turning

• [2] AND appears to be dying…
  – Irreversible decline
• [1] Acute **confusional** state
  – **Hyperactive delirium**
    – NICE CKS, 2016

• [2] **Variety** causes
  – **Drug** toxicity
  – Physical / psychosocial **symptoms**
  – **Multi-organ** failure / advanced tumour… “**dying**”

• [3] In **predicted final hours** and decision
  – (i) **Untreated** and / or
  – (ii) **Untreatable**
Delirium in palliative care
- Most prevalent neuropsychiatric complication
- Frequently overlooked / misdiagnosed by healthcare team
  » Coggins & Curtiss, Pall & Supp Care, 2013
  » Bush et al, Drugs, 2017
• [1] **Acute** and **fluctuating course**
  – Rapid onset (hours / a few days) varies (across day)

• [2] **Impaired conscious level**…
  – Disturbed **attention** (focus) / **awareness** (orientation)
  – Less awake and less aware

• [3] **Confusion**
  – **Cognitive** impairment
  – E.g. memory, language, perception / visual hallucinations

• [4] **Consequence** of **disease(s)** or **treatment(s) / toxins(s)**
  – Cannot be better attributed to another diagnosis
    » DSM V, 2013; NICE CKS, 2016
Why Not Use “Delirium” with Patients / Families and HCPs …?

• **Delirium** is NOT liked by patients, family, public…?
  – Not as neat as “agitation”, “restlessness”
  – Clinical jargon… less understandable
  – Less palatable, discriminatory stigma mental health

• **Delirium** is NOT liked by all clinicians…?
  – Not wanting to medicalise natural dying process
  – Delirium screening – futile / burden patient / staff
  – Risks over-investigate – no meaningful answer
  – Risks over-treat – no meaningful response
Is Terminal Agitation One, Two or All Three Sub-Types Delirium…?

• [1] Hyperactive delirium
  – Most recognisable – most diagnosed NOT most common
  – Restlessness / agitation, rapid mood changes, hallucinations, refusal to cooperate with care… emotive

• [2] Hypoactive delirium
  – Most missed, even induced…?
  – Most common >75% palliative phase (NICE CKS, 2016)
  – Reduced motor activity, sluggish, drowsy, or ‘in a daze’
  – Withdrawn, quiet, sleepy… NOT emotive

  – Most common overall – features of both hyperactive and hypoactive delirium, can switch quickly to / from one to other
Dying: Terminal Has All Three Sub-Types Delirium…?

Hyperactive

Mixed

Hypoactive

©Gannon, 2019…!
Terminal Agitation and the Three Sub-Types of Delirium

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- **[3] Mixed delirium**
  - Most common overall
  - Features of both hyperactive and hypoactive delirium, can switch quickly to / from one to other

Patient experience of delirium… distressing even with hypoactive delirium

Bush et al, Ann Oncol, 2018
Causes Delirium...
Any Chronic Predisposing Factor

- Persisting severe acute illness
- **Frailty** / multiple comorbidities / severe chronic illness
- Sensory – visual / hearing impairment
- Immobility / limited mobility
- >65 years / >70 years
- **CNS disorder** e.g. dementia / CNS tumour 1’ / 2’
Causes Delirium…
Any Acute Precipitating Factor

- Drugs / alcohol / illicit; toxicity / polypharmacy / withdrawal
- Lack of / over stimulation… change to environment
- Urinary retention / constipation
- Increased sensory impairment
- Hypoxia
- Dehydration, electrolyte imbalance
- Pain
- Infection
- Sleep disturbance
- Immobility / limited mobility
- Poor nutrition / deficiencies
- Intracranial event / malignancy
- Acute organ failure / exacerbation chronic illness
- Surgery / hip fracture
- Dying
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Prospective study on SPC IPU advanced cancer patients with delirium
Median 3 (1-6) causes / episode
- Bush et al, 2017
Causes Delirium…
Hospice Cascade / Domino Effect
Causes / Contributors to Terminal Agitation in Hospices #1

- **Drug** toxicity; S/E, excess dose, accumulation, interactions
  - Opioids, benzodiazepines, steroids, antipsychotics, anticonvulsants, anticholinergics, antihistamines
  - Drug interactions…
  - Illicit drugs / alcohol… missed, prevalence >10-20%…?

- **Drug** withdrawal
  - Sedatives, antidepressants, alcohol, nicotine, illicit

- **Lack of / over stimulation**…
  - Change of environment / room / staff
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Causes / Contributors to Terminal Agitation in Hospices #2

- GIT / GUS
  - Constipation, urinary retention
  - Urinary catheter

- Increased sensory impairment
  - Visual / hearing impairments (aids / ear wax…!)

- Metabolic disorders
  - Liver / renal impairment
  - Hypercalcaemia, hyperglycaemia, uraemia, hyponatraemia
  - Hypoxia
  - Dehydration and malnutrition
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Causes / Contributors to Terminal Agitation in Hospices #3

- Uncontrolled pain / discomfort
  - Tumour, *re-position, restraints, immobility*
  - *Too hot, too cold, wet* bed

- Infection
  - Inflammatory response, pyrexia…
  - *UTI, LRTI*

- Raised intracranial pressure, brain damage / dysfunction
  - Brain tumours / cerebral *metastasis*
  - Underlying *dementia* (diagnosed but *often not*)
  - Cerebral infarction / haemorrhage
    » NICE, 2010(2019); NICE CKS, 2016
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    » NICE, 2010(2019); NICE CKS, 2016
Delirium…
Prevention is Better than Cure…?
Evidence: Non-Drug Treatment Prevents Delirium…

- **Multi-component** intervention
  - Physical activity
  - Cognitive activity
  - Sleep
  - Hydration
  - Vision and hearing
- ‘**Considerable** evidence’ effective **preventing** delirium
  - RCT, meta-analysis (n=4,267) / Cochrane review (n=16,082)
  - Reducing delirium incidence **by around one-third**
    » Bush et al, Ann Oncol, 2018; Hosie et al, bmjopen 2019
Evidence: Non-Drug Treatment Prevents Delirium… But…!

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But how applicable…?
- Delirium is NOT always terminal agitation...
- Hospital inpatients (likely reversible pathology)
- Terminal agitation will be in 2/3rd non-responders…?
Evidence: Non-Drug Treatment Prevents Delirium… Enough…?

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  - Cognitive activity
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  • **But** how applicable…?
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**NOT** always ‘prevent’ delirium…
But may still **delay onset**…
And may be **less severe**…?
Anticipatory de-prescribing; wean before lose oral route
  - Number AND dose of drugs…
    • Prevent abrupt withdrawal e.g. SSRI / Pregabalin
    • Correct misguided opioid escalation
  - Address physical, emotional, social, spiritual needs…!!!
    - Pre-emptive patient able to benefit, prepare patient / family
    - Don’t transfer for EoLC, move nearer nurses station…?!
    - Don’t move just for pressure sore targets
    - Don’t leave catheter in as dies
Logical Approach to Management of Terminal Agitation…

Maybe NOT...?
[1] Assessment of Possible Terminal Agitation

- Make **diagnosis** / check for potential **reversibility**
  - For both [1] **deterioration** and [2] **delirium**

- History – symptoms
  - Patient and informants

- Medications
  - Still taking and recently **stopped**
  - Alcohol, smoking, **illicit**…

- Examination – signs
  - Bladder and bowel…
  - Hydration, sepsis….

- Investigations
  - Bloods, microbiology, O2 sats, glu BM…

- **Mainstay** is… as per any **delirium**
  - Manage **underlying cause(s)**
  - Establish **diagnosis / prevention / treat** as best as can
    - NICE, 2010(2019); NICE CKS, 2016
  - **Must** treat **potential reversibility**
  - **Unless** valid and applicable **ADRT / formal Best Interests**

- **Mainstay** is... as per any delirium
  - Manage underlying cause(s)
  - Establish diagnosis / prevention / treat as best as can

Palliative Care **20%-50%** delirium episodes reversed; (1) drugs, (2) infection, (3) abnormal electrolytes
- Bush et al, Drugs, 2017; Bush et al, Ann Oncol, 2018
Mainstay is... as per any delirium

- [1] Manage underlying cause(s)
- Establish diagnosis / prevention / treat as best as can
- Must treat potential reversibility

Unrealistic, not applicable...?

By definition NOT ‘reverse’ terminal agitation
• **Reversible** delirium and **irreversible** delirium share very similar clinical presentation.

• Paradox, delirium linked **both** to…
  – (1) Terminal phase (**irreversible**)
  – (2) **Reversible** dip in trajectory

• Challenge for clinicians, patients, family
  – (1) Unduly **fatalistic** – miss reversibility
  – (2) Overly **aggressive** – over-**medicalised** dying
    » Bush et al, Drugs, 2017

**BUT… [1] How Know if **this** Delirium is **Reversible** or Not…?**

Get it just right…!
AND... [2] ‘Reversibility’ Can Be Relevant in Terminal Agitation...?

Even if irreversible, why make it worse...?

Delay onset / less severe
AND... [2] ‘Reversibility’ Can Be Relevant in Terminal Agitation…?

Even if irreversible, why make it worse...?

Families hugely appreciative of delirium reversal or part reversal, even short period, to allow meaningful communication

Bush et al, Drugs, 2017

Delay onset / less severe
• **De-prescribing** review / reduce **drugs**
  - Stop / wean non-essential drugs (opioids, sedatives, steroids)
    • **Opioid** toxicity common, ~1/3rd, more elderly
    • Exclude opioid **neurotoxicity** (drowsy, agitated, myoclonus)
    • **Reduce** opioid dose by 1/3 to 1/2, consider **switch** – Alfentanil
      » Bush et al, Ann Oncol, 2018

• **Address infection**
  - Realism; PO vs IV, blind ABx, in isolation, irreversible dying
    » NICE, 2010 (2019); SIGN, 2013; NICE CKS, 2016

• **Optimise** **oxygen** saturation

• **Peri-tumour** **oedema**
  - Dexamethasone 4–8 mg or more, daily in divided doses
    » Bush et al, Drugs, 2017
• Maintain **hydration / nutrition**
  – As far as **appropriate**, e.g. check dentures
  – Actively manage dehydration (consider **24h fluid trial**… S/C)

– CAH 1L vs. 100ml / day **reduced delirium** (Memorial Delirium Assessment Scale: 1 vs. 3.5: P=0.084 **>90% chance real**…!)
  » Bruera et al, J Clin Oncol, 2013

– CAH may **delay**, but not prevent delirium (data needs caution)
  » Davies, et al, Pall Med, 2018

– Last days of life (NICE) CAH may:
  • **Relieve** distressing symptoms or signs vs. cause **overload**
  • Uncertain if **prolong life / dying** or **hasten death**
  » NICE, 2010 (2019); SIGN, 2013; NICE CKS, 2016
Patient with Established Delirium

...Non-Drug Management

- **Non-drug** strategies *fundamental* role in delirium, should be *optimized* through whole MPT
  - Bush et al, Drugs, 2017
  - Star & Boland, Clin Med, 2018
Non-Drug Management …Comes Before Drugs

- Non-drug management of delirious patients
  - Makes more sense; best targets pathology…?
  - High staff resource; both physical and emotional cost…

- Attempts re-normalisation signals to brain…
  - [1] Environment; quiet, safe, familiar people, familiar place
  - [2] Body; daily functions
  - [3] Mind; reorient, reassurance
Normal High-Functioning Brain

- **Normal conscious** behaviours depend nuanced interaction
  - [1] Environment; 5 senses
  - [2] Body; feedback
  - [3] Mind; subconscious
**Delirium Low-Functioning Brain**

- **Normal conscious** behaviours depend nuanced interaction
  - [1] Environment; 5 senses
  - [2] Body; feedback
  - [3] Mind; subconscious

- Higher brain function disrupted by **toxic state of delirium**
  - Random…
  - Automated…
  - Primitive…
Chaos When Filter Broken Allows Wrong Context to Consciousness

Environment

Body

Unconscious

sound

smell

taste

touch

sight

memory

hopes

fears

hunger

body position sense

breathing

pain

People in Uniform

Cannot move

Delirium

Traumas from war

Averil Stedeford, 1984
Bed-bound on Ward, Becomes Held Captive by Soldiers…!

Averil Stedeford, 1984

Environment

Body

Unconscious

sound

smell

taste

touch

sight

pain

hunger

body position sense

breathing

memories

hopes

fears

Delirium

[1] Non-Drug

[2] Non-Drug

[3] Non-Drug
Logical to Avoid CNS-Acting Drugs in Terminal Agitation...

Environment

Body

Unconscious

sound

smell

taste

touch

sight

pain

hunger

body position sense

breathing

Increased

distress

memories

hopes

fears

NOT drugs

Averil Stedeford, 1984
Address Potential Harmful Signals from [1] Body

- Address urinary retention / constipation
- Address sensory impairment; ear wax, hearing / glasses
- Address / don’t cause pain
  - Assess / tailored pain management…
  - Non-drug… avoid catheter, lines
- Try to maintain normal sleep-wake cycle
  - Discourage napping, engage / bright light exposure in day
  - Quiet, uninterrupted, low-level lighting at night… melatonin…
- Maintain / normalise mobility
  - Active range-of-motion exercises / supported walking
    » NICE, 2010 (2019); SIGN, 2013; NICE CKS, 2016
    » Bush et al, Drugs, 2017
Address Potential Harmful Signals from [2] Environment

- Adequate **lighting**, clear signage
- Visible clock / calendar
- Environment **quiet** area, side room
- **Limit staff changes**
- If can, **remove catheter**, lines etc…,
- Remove physical restrains, **avoid cot sides** (low bed)
  » NICE, 2010 (2019); SIGN, 2013; NICE CKS, 2016
• Manage cognitive impairment / **disorientation**
• Talking; gentle repeated **reorientation, don’t confront**
• Effective communication / **reassurances**
  – **Repeated** minimum 3 times / day RTC, plus PRN
  – Where they are, who they are, and what your role is
  – Cognitively-stimulating activities e.g. reminiscence
    » NICE, 2010 (2019); SIGN, 2013; NICE CKS, 2016
Explain cause, likely course to patient, relatives, carers
Involve family, friends, carers to reassure / regular visits
Exposure to familiar objects i.e. from home
Address anxiety; delirium often very frightening
Agitation;
  – Use verbal / non-verbal de-escalation techniques
  – Think - discomfort, thirst, or need for toilet
  – Active listening, effective verbal responding, pictures, symbols

» NICE, 2010 (2019); SIGN, 2013; NICE CKS, 2016
Non-Drug Palliative Management Comes Before Drugs in EoLC…?

- Non-drug strategies… intuitively integral but effectiveness in final hours / days is unclear…?
  » Bush et al, Drugs, 2017
Managing Terminal Agitation in Hepatic Encephalopathy

- Case reflection
Background

- Man in 50’s
  - 3-year history **hepatocellular carcinoma**
  - Admitted hospice from hospital for terminal care
  - So agitated in ambulance required **rapid blue-light transfer**
- Terminal agitation, **delirium** – **hepatic encephalopathy**
  - Haloperidol 1mg nocte
  - Lactulose / ‘encephalopathy’ medications not helped
- On admission **initially settled [1]** sitting out in **chair**
  - Awake and confused
  - **Night-time**, ‘put to bed’ **restless and agitated**, wandering around / sitting on other patients’ beds
  - **Aggressive towards nursing staff** at night when changing leaking catheter
Medication First Night…
Didn’t Really Help…

- RTC – Haloperidol 1.5mg BD S/C
- PRN – Haloperidol 1.5mg S/C agitation, distress / aggressive behaviour preventing care
- PRN – Midazolam 2.5mg S/C (after medical advice) to facilitate catheter change
• Remained agitated until [2] wheelchair / wheeled around
  – Rapidly **settled in motion** but **agitated when static**
  – Longer periods settled, increasingly outlasted movement
  – Agreed to / window to wash / bath patient after **many weeks** of **refusing** personal care
  – Following bath, went back to needing to being wheeled around the hospice in wheelchair

• Appeared to be **dying**
  – Haloperidol 1.5mg S/C BD + PRN no help – **stopped**
  – Switched CSCI Levomepromazine 50mg + Midazolam 10mg
Terminal Agitation Fully Addressed by Wheelchair

- Calm / settled if wheeled around hospice – for many hours
- RTC – no increase in CSCI medications – only 50% in...
- PRN – no extra doses antipsychotics or benzodiazepines
- No response seen to drugs
- ‘Settled’ later in night, even allowed move him to bed
- Died peacefully the next morning
Terminal Agitation Fully Addressed by Wheelchair

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Result...
Wheelchair 1
Drugs 0
CNS-Acting Drugs as Symptom Control are NOT Logical …?

- Pharmacological treatment such as antipsychotics or benzodiazepines should be avoided, if possible
  » NICE CKS, 2016
Drugs Common But NOT a Logical Approach…?

- **NOT symptom control** / not addressing patient ‘complaints’
  - Fear losing control, impending doom / death, unresolved issues
  - Paranoia, hallucinations…
- Drugs make patient’s **symptoms worse**
  - Increase delirium / absence of awareness is **not sense of relief**
- Drugs may make **signs better** or worse…?
  - Managing **signs** for **family, friends and staff**
  - **Quick and easy**, meets misplaced expectations…?

Just say no…!
Doing the Wrong Thing **More** Often Doesn’t Make it Right…?

*The definition of insanity is repeating the same behaviors and expecting a different outcome.*

*Albert Einstein*
Association is **NOT** Causation…

Our Experience Misleads Us

Terminal Restlessness: Delirium, Dying and Drugs…

Level of Agitation / Distress

Timeline, hours / days / weeks
Sadly, Little Credit if Any… Would Look Better Anyway …?

Terminal Restlessness: Delirium, Dying and Drugs…

Level of Agitation / Distress

Timeline, hours / days / weeks

Panic...!

Drugs

Drugs

Relief...!
We Abandon Logic: “Just Give More”…!

If drug appears to work... **CAN** then give more...

If drug doesn’t appear to work... **MUST** give more...
Drugs Lack Evidence
No Drug Therapy for Delirium in Terminally Ill Adult Patients

- Drugs are opinion NOT ‘evidence’ based
  - Indefensible vs. unavoidable...?!

- **No medication** licensed for delirium, all ‘off-label’
  » Bush et al, Drugs, 2017

- **No adequate clinical trials** evidence to support drugs
  - “Insufficient evidence to draw conclusions for drugs in delirium in at end of life”
  - Yet suggested… “should follow current clinical guidelines”
    » Candy et al, Cochrane Review, 2012
Antipsychotics Lack Evidence

• **Antipsychotics** for prevention / treatment of **delirium**
  – **Systematic review and meta-analysis**
  – Evidence does **not support** use of antipsychotics

• **No high-quality evidence** to support antipsychotic drug use in treating symptomatic delirium in palliative care
  » Star & Boland, Clin Med, 2018
Antipsychotics Lack Evidence… Best of a Bad Lot…!

• “Relevant studies” 2000-17, cumulative n=881 (3/15 RCT)
  – Antipsychotics (I) – no demonstrable benefit
    • Risperidone; haloperidol
  – Antipsychotics (II) – may offer symptomatic benefit
    • Olanzapine; quetiapine; aripiprazole
  – Psychostimulant – may improve cognition if hypoactive
    • Methylphenidate
  – Benzodiazepines – sedation / anxiolytic not delirium…!
    • Midazolam; lorazepam
  – Opioid switches – efficacious if opioid-associated delirium
    • Fentanyl / various opioids to methadone, morphine to fentanyl
      » Bush et al, Ann Oncol, 2018
Antipsychotics Many Adverse Effects Including Delirium…!

- Variations in receptor affinities, vary SE profile across;
  - EPSE; dystonia, akathisia, parkinsonism, tardive dyskinesia
  - Sedation
    - Anticholinergic; blurred vision, dry mouth, constipation, urinary retention, tachycardia, confusion
    - Hypotension / dizziness (adrenergic)
    - Lowered seizure threshold
    - QTc prolongation
    - Neuroleptic malignant syndrome (NMS)
Evidence of Harm From Antipsychotics in Palliative Care

- **Double-blind, RCT** palliative care patients with delirium
- Risperidone, haloperidol or placebo
  - Adequately powered, \( n=247 \), intention-to-treat analysis
  - Individualized **supportive care** reduced **severity / duration** of distressing **symptoms** compared risperidone or haloperidol
  - Both **drug arms** significant more **extrapyramidal** side effects
  - Both **drug arms** significant more **rescue** midazolam
  - Non-significant **survival disadvantage** with haloperidol

- Patients ‘spared’ haloperidol, less distress and lived longer
- Advised **caution with antipsychotics** used delirium
  » Agar et al, JAMA Intern Med, 2017
• Might not be representative
• 1 trial – one standardized, 3-day regime, lower doses
• Cancer only…
• Oral solution i.e. excluded participants unable to swallow
• Mild-to-moderate delirium baseline i.e. not severe
• Irreversible and reversible causes combined
• Not matched – haloperidol arm more opioid toxicity risk where adding drugs likely counterproductive…?
Current Drugs Do “Not Improve” Delirium at End of Life

- Advanced cancer (n=218)
- Haloperidol most frequent
- Hypoactive delirium worsened in 56%
- More likely deteriorate after drugs if:
  - (i) Death expected within a few days
  - (ii) Organ failure
- Study not support current drug treatment of hypoactive delirium in palliative care setting
- Drug treatment for delirium not recommended, especially if close to death / organ failure
  » Okuyama et al, The Oncol, 2019
Medications with Potential Role in Delirium…?

- **Not yet recommended** lacking limited evidence e.g.
  - Methylphenidate
  - Modafinil
  - Valproic acid
  - Gabapentin
  - Ondansetron
  - Melatonin

  » Bush et al, Drugs, 2017
Why Do We Use Haloperidol…?

• When no help and high side effects…?
  – “we just do…!”

• Haloperidol seen as ‘practice standard’ for delirium in palliative care
  – Familiarity… always used it…!
  – Multiple routes, especially subcutaneous route
  – Emergency psychiatric use, with benzodiazepine, in psychosis-induced aggression for rapid tranquilization
    » Bush et al, Drugs, 2017
Treatment is Cultural NOT Clinical

- **Different** approaches in **different** countries…

- Systematic variation in end-of-life care sedation practice across UK, Belgium and Netherlands
  - Debated practice; continuous sedation till death when refractory symptoms in terminal cancer

- Qualitative interview study
  - 57 physicians / 73 nurses
  - 3 European countries
Drug Choice and Dose is Cultural... NOT Clinical

- [1] UK mainly low doses sedatives, rarely deep sedation
- [2] Belgium mainly deep sedation, at patient's request
- [3] Netherlands deep sedation as medical decision because request and refractory symptoms
  - » Seymour et al, Pall Med 2015
Audit of Management of Agitation in Last Weeks of Life

- Distressing and common
- Evidence for management poor

- **185 patients** across 11 settings in UK
  - Hospice 55%, Hospital 30%, Home 12%

- Majority died **within 3 days**
- Main reversible causes:
  - Pain
  - Breathlessness
  - Constipation
  - Urinary retention
Audit of Management of Agitation in Last Weeks of Life

- Non-drug
  - Psychological & spiritual support / communication

- Drugs at death
  - **Midazolam** (n=146) mean 26mg, 0-60mg
  - **Levomepromazine** (n=61) mean 56.8mg, 5-250mg
  - **Haloperidol** (n=25) mean 3.5mg, 1-8mg
  - **Phenobarbital** (n=9) mean 922mg, 200-1200mg

» Nolan, et al bmjspcare, 2018
Hospice Use of Anxiolytics and Antipsychotics in Dying Phase

• **Audit** of 2 UK hospice IPU’s (n=75)
  • Anxiolytics and antipsychotics widely used
    – Nearly all inpatients during last week
    – 82.1% (n=32) and 91.7% (n=33)
  • Most common indication
    – *Terminal agitation* (n=16, 50%)
    – Mixed terminal agitation and delirium (n=11, 33.3%)
  • Drugs; variations in indications, drugs and doses
    – *Midazolam* used most (77.8%, n=28, to 74.4% n=29)
    – Haloperidol more at 1, Levomepromazine more other
    – **No patients received Phenobarbital**
      » Hawkins & Sills, bmjspcare, 2017
Hospital Audit of Opioids and Sedatives in Last 24 Hours

- Australian tertiary hospital
- Audit of 102 patients identified as ‘dying’

- Mean dose midazolam 6.0mg (1/3<sup>rd</sup> NZ study)
- Mean dose morphine 56.5mg (20% more NZ study)
- Haloperidol… not featured…!

Delirium has multiple stakeholders…

Patient
- Increased mortality… (when not part of fatal episode)
- Significant physical morbidity
- Severely *distressing* experience

Families
- Severely *distressing* experience

Professional caregivers
- Severely *distressing* experience
  » Bush et al, Ann Oncol, 2018
At End of Life…
Don’t Just Focus on Patient…!

- DON’T forget **carers**
  - ‘Most’ in **need**
  - Most ‘able’ to **help** (2-way)
Needs of Carers of Palliative Care Patients with Delirium

- Literature review
- Carers have high levels of **distress** with delirium
  - Fear, anger, disappointment and sadness are common
- Uncertainty if ever **re-establish relationship** before death
- Carers **contribute** to delirium management
  - (i) Prevention and detection (ii) Acting as patient advocates
  - (iii) Assist monitoring patient symptoms
- Carers desire more **information / advice** how to behave
- Reducing caregiver distress as **goal** of future interventions
  » Lugton et al, bmjspcare, 2015
  » Finucane et al, Psycho-Oncology, 2017
Needs of Carers of Palliative Care Patients with Delirium

- Literature review
- Carers have high levels of distress with delirium
  - Fear, anger, disappointment and sadness are common
- Cares contribute to delirium management
  - (i) Prevention and detection
  - (ii) Acting as patient advocates
  - (iii) Assist monitoring patient symptoms
- Cares desire more information/advice on how to behave
- Reducing caregiver distress as goal of future interventions
  - Lugton et al, bmjspcare, 2015
  - Finucane et al, Psycho-Oncology, 2017

Delirium information leaflet/brochure for relatives to improve understanding/ preparedness; ameliorate some distress/increasing competence/confidence
  - Bush et al, Ann Oncol, 2018
At End of Life…
Don’t Forget Staff…!

- DON’T forget **staff**
  - Also in **need**
  - Battling pressure **to fix** = need to **prescribe**
Terminal Agitation…
Difficult Features for Staff

- Distressing; witness patient agitation
- Distressing; witness family distress
- Evening / night worse; needs more, when less staff
- Aggression / shouting; disturbs others / safety issues
- Paranoid / challenging; blaming staff, refusing care
Needs of Palliative Care Staff Caring for Patients with Delirium

- **4 themes** staff experiences of *terminal agitation* in hospice
  - [1] Personal
  - Challenge staff confidence in symptom control
  - [2] Causes
  - Only document *biomedical* despite wide range
  - Pressure from relatives / within teams to "do something" – give medication for reasons other than just agitation
  - [4] Discordant narratives
  - Relatives and staff disagree on presence or absence agitation

- **Subjective** identification, cause and management
  » Tempest, bmjspc, 2014
Needs of Palliative Care Staff Caring for Patients with Delirium

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- **Subjective** identification, cause and management
  - Tempest, bmjspc, 2014

Nurses / healthcare team should be offered formal team debriefing session after challenging cases
- Bush et al, Ann Oncol, 2018
When Ongoing Sedation Appears Necessary…

“Which would you prefer, prozac or a stiff whisky?”
Drugs Do Come After Non-Drug Management

First do no harm
Second do good
Third “net gain”

How defined...?
Drugs are Last Resort, When…

- **Severe** agitation or psychosis, *and*
- Verbal/non-verbal de-escalation inappropriate / failed, *and*
- **Danger to themselves or others**, *and*
- Cause of delirium is known / being treated, *and*
- The **benefit outweighs the risk** to the person, *and*
- One-to-one supervision, so **continually monitored**

» NICE, 2010 (2019); NICE CKS, 2016
Drugs are **Last Resort**, When…

- **Severe** agitation or psychosis, *and*
- Verbal/non-verbal de-escalation inappropriate / failed, *and*
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» NICE, 2010 (2019); NICE CKS, 2016

**Irreversible delirium and dying…**

1. Agitation so severe **drugs cannot make worse**, *or*…
2. Family / staff at **breaking point**, *or*…
3. **Danger** to themselves or others
Refractory Delirium in the Actively Dying Patient

Irreversible delirium *and* dying...

1. Agitation so severe *drugs cannot make worse*, *or*...
2. Family / staff at *breaking point*, *or*...
3. *Danger* to themselves or others
• Delirium treatment in EoLC failing / no window for more
  – Non-drug measures all in place
  – Targeted, titrated doses inadequate…?
• Time to U-turn
  – Escalating psychosocial crisis, as dies
  – Shift focus to family / staff
  – Unavoidable transition palliation to sedation…?
• If sedation, remember…
  – Different ethics
  – Different drugs / doses
  – Different presentation…!
Refractory Delirium in the Actively Dying Patient

• Delirium treatment in EoLC failing / no window for more
  – Non-drug measures all in place
  – Targeted, titrated doses inadequate…?

• Time to U-turn
  – Escalating psychosocial crisis, as dies
  – Shift focus to family / staff
  – Unavoidable transition palliation

• If sedation, remember…
  – Different ethics
  – Different drugs / doses
  – Different presentation…!

Is this where we get mixed up…?
Unavoidable (Uncomfortable) Shift of Focus as Death Nears…?
Let’s **Drop** the Made-Up Term **Terminal Agitation…?!**
Reverse Reversible, Relieve Relievable, Mask Unrelievable...

- **Sedation does not alleviate**, but merely **masks suffering**

Sounds good...!

Sounds bad...!

- Need clear **objectives** for drugs in delirium in EoLC
  - *Cannot say*; aim is to calm agitation (not sedate) when…
  - *Reality; reduce movements* (and hope less aware…?)
- Duty of candour – be realistic
  - **Prepare** family / staff; **significant risks and limited benefits** of medication must be discussed / ‘informed consent’
    » NICE CKS, 2016
  - Explain inherent **risks**, may make patient **worse**…
  - **NOT** symptom control, not reduce perceptual disturbance
- Review frequently
  - Titrate **down** as well as **up**
  - **Withdraw** if not helping – **NOT** spiral up
Need clear **objectives** for drugs in delirium in EoLC
- *Cannot say*; aim is to calm agitation (not sedate) when…

Judicious, proportionate **sedation** for a more ‘peaceful’ death
1. (Reduce patient distress) - unlikely…?
2. Reduce **family** distress
   - Bush et al, Drugs, 2017
3. Reduce **staff** distress
   - Titrate **down** as well as **up**
   - **Withdraw** if not helping – **NOT** spiral up
Crucial Ethical Positioning of Ongoing Sedation...

- Sedation is **not a good** in itself...
  - Denies opportunities
  - Lose **potential** for ‘lucid windows’

- Sedation can be a **means not an end**...
  - No net gain in patient health / well being
  - Autonomy is lost from that point
    » Willis et al, Pall Med, 2014
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- Sedation can be a **means not an end**…
  - No net gain in health / well being
  - Autonomy is lost from that point

> Willis, et al, 2014

Iatrogenic lowering of consciousness may be **unavoidable**, may be **necessary**, may be **common**, but this **doesn't make it desirable**
Summary: NOT Terminal Agitation

- **Catastrophic** body failure as dies
  - Not discrete diagnosis
  - Significant *distress* common, all stakeholders…
  - Inevitable – must re-frame *expectations*

- **Before final hours** manage as *delirium*
  - Assessment key; don’t under-estimate *hypoactive delirium*
  - Reversibility; don’t dismiss, reverse or delay, reduce
  - Avoid / remove causes of agitation
  - Good evidence *non-drug interventions*, must do better
  - Weak evidence *drugs*, net harm, must do less harm

- **In final hours** – manage as ‘dying’
  - U-turn *family / staff*; antipsychotic, benzodiazepine etc…?
Delirium vs. Terminal Agitation
What’s Hospice IPU Approach…?

- **Ensure** patients are…
  - Hydrated
  - Avoid unnecessary catheterization
  - Optimize sleep hygiene
  - Encourage mobilization
  - Avoid sensory deprivation
    - Appropriate lighting
    - Use of hearing and visual aids
  - Use verbal orientation / devices
    - Visible clock and orientation board
      » Bush et al, Drugs, 2017
Delirium and Terminal Agitation
New Hospice IPU Approach...?

• **Ensure** patients are...
  ✓ – Hydrated
  ✓ – Avoid unnecessary catheterization
  ✓ – Optimize sleep hygiene
  ✓ – Encourage mobilization
  ✓ – Avoid sensory deprivation
    • Appropriate lighting
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  ✓ – Use verbal orientation / devices
    • Visible clock and orientation board
      » Bush et al, Drugs, 2017
Honesty – Realism

• “We cannot take away the hard thing that is happening, but we can help to bring the burden into manageable proportions”

  » Cicely Saunders, 1963
Not ‘Perfect’ at the End, But…

As Comfy as Can, Just As Before

Pain ESAS at death on Acute Palliative Care Unit:

a) Severity 3/10
b) Prevalence 40%

Hui et al, JPSM, 2015
More Informed... More Realistic...? We Cannot Get 100% Relief

Earlier...
Morphine only *some* pains and only *half* patients get above *50%* relief

Very end of life...
Morphine for *any* distress, *all* patients, expect *100%* relief...!

Death is hard
The ‘Real World’ Warts and All

Sanitized; all nice
Hospice Rose-Tinted Glasses
In Practice... Drug Doses in Terminal Agitation
Drug Management if Essential [1] Haloperidol

- First-line: antipsychotics
- **PRN 1st**, NOT regular
- **Use lowest** clinically appropriate dose

- Haloperidol 0.5-1.5mg PO / SC, PRN
  - Most established, safe in short term use
  - One of least sedating / most anti-dopaminergic
  - Low dose RTC / “maintenance” may be unavoidable
  - 0.5-3mg PO / SC, OD / BD or CSCI

- Switch levomepromazine
  - More sedating / risks postural hypotension
  - If **2nd-line** 12.5-25mg SC, OD / BD or CSCI
Drug Management if Essential [2] Midazolam

- Second-line: benzodiazepines
  - No...! Treatment-limiting adverse effects without any benefit
  - Only if clear usual doses of Haloperidol not helping
  - Yes...! Specific; anxiety; alcohol withdrawal; Parkinson's disease; dementia with Lewy bodies

- PRN 1st, NOT regular
- Use lowest clinically appropriate dose
  - Lorazepam 0.5-1mg PO / SL 6-18 hourly
  - Midazolam 2-5mg SC 1-2 hourly
  - Diazepam 5mg PO / PR 6-12 hourly

- Low dose RTC / “maintenance” may be unavoidable
  - Midazolam CSCI 5-30mg/24h
Drug Management if Essential [3] Sedation… the U-Turn

- Third-line; switch / increase / combine higher RTC doses
  - Titrate Haloperidol, Levomepromazine, Midazolam
  - Severe cases patient risk themselves or others +/- crisis
- Not symptom control – chemical restraint… cultural…
- No evidence, not clinical, lacks logic, but necessary…?
  - Only if clear irreversible rapid decline (dying) / delirium
  - Titrate cautiously, only if clear consistent dose response
  - And, only if clear pre-determined net gain / no toxicity
- Phenobarbital; load 200mg IM / CSCI 800mg-1600mg/24h
  » Allan et al, bmjspcare 2018
- Consider Propofol…?
We’ve Made It…!

Richard Carapaz, Movistar, in Rome, *Giro d'Italia*, 2019

Egan Bernal & Geraint Thomas, Team Ineos in Paris *Tour de France*, 2019

Primoz Roglic, Jumbo-Visma *La Vuelta a España*, 2019
Thank You... Discussion

A sleeping, not sedated, animal...!
Terminal Restlessness: Important to Not Fan the Flames

More CNS-acting drugs doesn't mean better, indeed, patient will be predictably worse...
Logical Approach to Drug Treatment

- Pain [opioid-responsive]
- Pain [non-opioid-responsive]
- Anxiety
- Cerebral irritation
- Existential distress
- Dyspnoea
- Delirium [drug-induced]
- Delirium [sepsis]
- Delirium [biochemical]
- Dementia
- Mixed

- Titrate opioids while responds
- **Avoid** opioids
- Titrate anxiolytics
- Titrate anti-epileptics
- ? Anxiolytics
- ? Cautious titrate opioids
- **Reduce** sedative drugs
- **Avoid** sedative drugs
- **Avoid** sedative drugs
- **Avoid** sedative drugs
NOT... Give Random Anything, till Patient Flat...?

Priority = symptom control

- Pain [opioid-responsive]
- Pain [non-opioid-responsive]
- Anxiety
- Cerebral irritation
- Existential distress
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- Delirium [drug-induced]
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- Dementia
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Priority = not sedate

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NOT... Give Random Anything, till Patient Flat...Unless Must...?

**Priority = symptom control**

- Pain [opioid-responsive]
  - Titrate opioids while responds
- Pain [non-opioid-responsive]
  - Avoid opioids
- Anxiety
  - Titrate anxiolytics
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- Delirium [biochemical]
  - Avoid sedative drugs
- Delirium [sepsis, other]
  - Avoid sedative drugs
- Dementia
  - Avoid sedative drugs
- Mixed

**Priority = not sedate**

First do no harm

Second do good

Third “net gain”
Ethical Stalemate with Ongoing Sedation in EoLC...

- Utilitarianism
  - Wider risks as looks like killed individual patient… avoid
  - It works and is expected, everyone’s happy, offer it

- Kant’s duty-based
  - Mustn’t let suffer, so must sedate
  - Must preserve ‘the person’ / life, so mustn’t sedate

- Virtue ethics
  - Only use if no other option…
  - There are always other options...?
• [1] **Non-sedating** use of medication
  – Within ‘normal’ **symptom control**
  – As much as **needed**

• [2] **Proportionate sedation**
  – **Time-limited** / intervention-specific – light / deep
  – Targeted, **careful** dose titration for a ‘very’ end-of-life crisis

• [3] **Ongoing supra-therapeutic** dose
  – Specific intent **anaesthetising** patient in advance of what may have proved a peaceful / uneventful death
    » Willis, Gannon, Harlow, Baker & George, Pall Med, 2014

Must Better Differentiate Good Care from Bad Practice
Must Better Differentiate Good Care from Bad Practice

• [1] Non-sedating use of medication
  – Within ‘normal’ symptom control
  – As much as needed

• [2] Proportionate sedation
  – Time-limited / intervention-specific – light / deep
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    » Willis, Gannon, Harlow, Baker & George, Pall Med, 2014
Why Don’t We (Only Some…?) Like Midazolam…?

- Palliative care HCPs **cautious** with benzodiazepines
  
  » Bush et al, Drugs, 2017

  - **Despite** same **concerns cause delirium** as antipsychotics
  - **Despite** same familiarity
  - **Despite** same multiple routes, including subcutaneous route
  - **Despite** same psychiatric emergency use with haloperidol in psychosis-induced aggression rapid tranquilization
  - And **USP** in alcohol / hypnotic withdrawal and Parkinson’s disease or DLB (unacceptable EPSE risk with antipsychotics)
Drugs Do NOT Address Patient Symptoms…

- **Patient experience** of delirium
  - Clouded thinking, confusion
  - Anxious / threatened / humiliation
  - Vivid hallucinations / illusions provoke overwhelming fear
  - Feel lack of control
  - A sense not being listened to / understood / isolation
  - **Distressing even with hypoactive delirium**
    » Bush et al, Ann Oncol, 2018; Hosie, bmjopen 2019