Neuropsychiatric complications of commonly used palliative care drugs

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ABSTRACT

For those facing progressive life limiting disease, symptoms across a range of systems can be problematic. Clinicians may find themselves prescribing from several classes of drugs to alleviate distressing problems and to maximise quality of life for patients. Many drugs used for symptom control in palliative care give rise to neuropsychiatric side effects as they affect the central nervous system either directly or indirectly. The common unwanted effects of these drugs are well known, but there are some important neuropsychiatric effects that physicians are less aware of. If unrecognised, these effects can generate considerable distress and unnecessary harm to patients. We aim to highlight some of the adverse neuropsychiatric effects which occur with commonly used drugs in palliative care. Antiemetics such as metoclopramide and haloperidol can cause significant levels of neuropsychiatric toxicity, as can opiates, antidepressants, anxiolytics and antipsychotics. The syndromes or entities that will be considered are delirium, drug induced parkinsonism, akathisia, serotonin syndrome and neuroleptic malignant syndrome. The intention is to alert clinicians to the iatrogenic complications which may ensue on prescribing drugs commonly used in the palliative care setting.

The emphasis of palliative medicine is to optimise symptom control and quality of life for patients who are living with terminal disease. Any drug interventions must consider the balance of risks and benefits to ensure that patients do not experience any added distress. Many drugs used for symptom control in palliative care exert unwanted effects on the central nervous system. Some of these drugs show adverse neuropsychiatric or other toxic effects when used alone, in combination with other drugs, when given in high doses or when given over a prolonged period of time. Some of these toxicities are common and some less so, but they are all significant and potentially very harmful, and can be fatal. Clinicians may not be aware of the less common conditions such as akathisia, serotonin syndrome and neuroleptic malignant syndrome, and so symptoms may wrongly be attributed to a patient's condition, managed incorrectly and thus exacerbate the distress experienced. In raising awareness of these pitfalls, we seek to aid the detection and initiation of appropriate management for these conditions, in the pursuit of excellent, holistic and informed end of life care.

DELIRIUM

Delirium is a clinical syndrome which is diagnosed when there is a disturbance in consciousness and

attention, with a change in cognition or perception. It usually develops over a period of hours to days, follows a fluctuating course and has evidence of an organic aetiology.^{1 2} It is frequently not recognised or misdiagnosed and is often poorly treated.³

Delirium is the most common clinical neuropsychiatric condition, occurring in 26–44% of admissions to hospitals or specialist palliative care units.² Prevalence of up to 88% before death has been reported in specialist inpatient units, and it may be reversible in approximately 50% of episodes.⁴ It is estimated that medications alone may account for 12–39% of all cases of delirium.^{5 6} Drugs that cause delirium include opioids, anti-secretory medication, anxiolytics, antipsychotics, antidepressant drugs, steroids and non-steroidal anti-inflammatory agents (NSAIDs) (table 1).⁷

The aetiology, diagnostic criteria, and management of delirium are covered in another paper in this series.¹

DRUG INDUCED PARKINSONISM

Drug induced parkinsonism (DIP), sometimes also referred to as pseudo-parkinsonism, is the second most common cause of akinetic rigid syndrome in the western world. Its prevalence is increasing due to an ageing population and the rise of polypharmacotherapy.¹¹ The syndrome has also been named neuroleptic-induced parkinsonism and antipsychotic-induced parkinsonism.^{12 13}

Incidence

Parkinsonism has a prevalence in the general population of around 7% in those over 50 years old.^{14 15} DIP has a population prevalence of 2.7%.¹⁵ In those over 60 years taking neuroleptics for psychiatric illness, prevalence of antipsychotic induced parkinsonism has been reported as exceeding 50%.¹³ Individual susceptibility to neuroleptics varies and the incidence of the syndrome increases with age. Antipsychotic dose and potency, a previous history of extra pyramidal signs and a previous history of dementia are the major risk factors for developing DIP.¹³ Most cases of DIP occur within the first 2–3 months of drug initiation.¹³ Although originally recorded as a side effect of neuroleptics, DIP has now been described with a wide range of compounds including antiemetics, antidepressants, calcium channel antagonists, antiarrhythmics, antiepileptics and cholinomimetics.^{11 16 17}

Pathophysiology

Positron emission tomography (PET) studies have shown that 80% or more cerebral D2 receptor

Table 1 Delirium inducing drugs commonly used in palliative medicine^{6–10}

Opioids	For example, morphine, fentanyl, oxycodone. The risk of delirium associated with opioids is dose related
Anti-secretory medication	For example, hyoscine hydrobromide (anticholinergic effect)
Anxiolytics	For example, midazolam, diazepam, lorazepam
Antipsychotics	Antipsychotics, especially those with an anticholinergic effect, can induce delirium, and all traditional antipsychotic drugs confer an increased risk Levomopromazine (methotrimeprazine/nozinan), a frequently used anti-emetic, has considerable anticholinergic properties and therefore presents a high risk of inducing delirium
Antidepressant drugs	All tricyclic antidepressant drugs exert an anticholinergic effect, with amitriptyline having the strongest and nortriptyline the weakest. The tricyclic antidepressants constitute a high risk group of drugs
Anticonvulsants	All anticonvulsants have been reported to induce delirium, although the mechanisms are uncertain with probable differences between different drugs
Steroids	Adverse central nervous system (CNS) effects associated with corticosteroid treatment include delirium and chronic cognitive impairment, the risk being dose related
NSAIDs	All non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to induce delirium
Gastrointestinal agents	Antispasmodics and H ₂ blockers
Antibiotics	Fluoroquinolones—for example, ciprofloxacin
Antihistamines	First generation—for example, diphenhydramine and chlorpheniramine

occupancy is consistent with the appearance of DIP. Occupancy of 40–70% of D2 receptors induces no DIP.¹⁶ Conventional neuroleptics such as haloperidol tend to induce high D2 receptor occupancy, whereas atypical neuroleptics cause lower occupancy rates and hence less DIP.

Clinical features

Bradykinesia is the earliest and most common sign, with muscular rigidity and disturbances of posture and gait developing later. Tremor is less apparent than in Parkinson's disease.¹⁶ Hypersalivation can occur. The development of these features is broadly dose dependent. Although traditionally considered reversible, DIP may persist after drug withdrawal.¹⁸ At least 10% of patients with DIP developed persistent and progressive parkinsonism even when the causative drug had been discontinued.¹¹

Special precautions are needed in the elderly, in patients treated with multiple potentially causative drugs for prolonged periods of time, and in those with familial parkinsonism or tremor.¹¹

Management

Monitoring patients in the early weeks of treatment will help early detection of DIP. Initial management of this disorder involves withdrawal of the causative drug(s). If discontinuation is not possible then a switch from a conventional to an atypical neuroleptic should be considered. If the drug(s) cannot be altered then it is advisable to add anticholinergic medication such as procyclidine. In the elderly, adding amantadine is recommended to prevent anticholinergic side effects.¹⁶

AKATHISIA

Akathisia is an idiopathic condition characterised by a state of restlessness and motor agitation most frequently observed in

Box 1: Non-neuroleptic drugs which cause akathisia²³

- ▶ Antiemetics: metoclopramide, prochlorperazine, [domperidone]
  - ▶ Antidepressants: tricyclics, selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline), venlafaxine, [nefazodone]
  - ▶ Calcium channel blockers: cinnarizine, flunarizine (also H₁ antagonists), [diltiazem]
  - ▶ Others: methyl dopa, levodopa, and dopamine antagonists, [lithium carbonate], buspirone, [anticonvulsants], [pethidine], [interferon α], [sumatriptan]
- [ ] = anecdotal or not well established evidence

association with antipsychotic drugs.^{19–21} It has also been observed with a number of other drugs, including antidepressants and metoclopramide.^{22–24} It was first described in 1909 by Hasvonec to describe restless patients suffering from hysteria and neurasthenia and is derived from the Greek term meaning “not to sit”.^{22–24–25} Box 1 provides a list of non-neuroleptic drugs which may cause akathisia. Neuroleptics and some of the other drugs listed in box 1 are commonly used in the palliative care setting and it is therefore important that the presence of akathisia is recognised to avoid unnecessary patient distress.

If the symptoms of akathisia are misdiagnosed as an exacerbation of agitation or psychosis, this might lead to an increase in antipsychotic medication which would serve to aggravate the problem further.^{21–23–26–27} Most research into this condition has been undertaken in the psychiatry setting; however, the recognition and treatment of akathisia is important in the palliative care population.²⁵

Incidence

The reported incidence rates for neuroleptic induced akathisia exhibit wide variation and this may reflect the lack of commonly accepted diagnostic criteria.²⁶ Prevalence is likely to be between 20–75%.^{22–28–29}

Pathophysiology

The underlying cause of akathisia is not well understood but may be related to dopamine blockade in the mesocortical dopamine pathway.^{20–22–30} Involvement of central serotonergic and adrenergic neurotransmitter systems has also been postulated.³¹ Risk factors for developing neuroleptic induced akathisia are not completely understood. Both drug dose and rate of increment of dose are important risk factors.^{24–28–32–33} Exposure to pharmacologically similar drugs, such as haloperidol, prochlorperazine and promethazine has been shown to confer an increased risk. Risk is also increased in patients who are concurrently taking morphine or sodium valproate.^{21–29}

Clinical features

There is a considerable amount of debate in the literature regarding the exact definition of akathisia. Most authors would agree that akathisia is part of the spectrum of extrapyramidal side effects.²⁰ Patients experience an inability to relax and are unable to tolerate being still. There is a subjective feeling of restlessness and objective motor agitation.^{21–26} The symptoms fall into a spectrum which in its mild form is characterised by incessant shuffling or tapping of the feet while seated and continuous shifting of weight and rocking of the trunk when

standing. In the more severe manifestations, akathisia can be exhibited as an inability to sit, stand or lie still, or as pacing or incessant running.^{19 22 26} The movement disorder is greatest in or restricted to the lower limbs.³⁴ The movements tend to be bilateral and symmetrical; however, there is no single motor feature pathognomic for the condition.^{20 35} Akathisia can therefore be considered to be a combination of restlessness, patient distress, tension and discomfort.

Akathisia usually has an onset of days to weeks after commencement of a causative drug.²⁴ It is imperative that the possibility of akathisia is considered when using these drugs so that treatment can be instigated without delay.³⁴ The *Diagnostic and statistical manual*, 4th revision (DSM-IV) research criteria in box 2 for neuroleptic associated akathisia can also be applied to akathisia caused by other drugs and is useful in diagnosis.

The Barnes akathisia rating scale (BARS) is a tool used to detect and monitor akathisia in patients treated with psychiatric medication. It measures both the motor features and the discomfort the patient experiences and is considered to be both reliable and valid.³⁶

Management

The best possible treatment is avoidance of potentially causative agents. In situations where this is not possible, it has been recommended that these drugs should be judiciously used and carefully monitored.²¹ The newer atypical antipsychotic drugs are felt to be less likely to produce acute akathisia and should therefore be used preferentially.^{22 32 38}

The clinician should have a high index of suspicion and if akathisia is thought to be present then the presumed causative drug should be discontinued or reduced.^{23 29} Symptoms should resolve within days of stopping the drug. If the patient is very symptomatic, there are a number of other drugs which can be used to counteract the symptoms. β -blockers are considered to be the most useful drugs in treatment.²³ Their mechanism of

action is thought to be adrenergic antagonism, which is beneficial because the adrenergic system is thought to exhibit overactivity as a result of dopamine blockade in this condition.²² Other drugs which have been used in treatment are benzodiazepines, cyproheptadine, and mianserin.^{19 22 24 39}

SEROTONIN SYNDROME

Serotonin syndrome, also referred to as serotonin toxicity, is a medication induced disorder which is the result of excessive serotonergic activity, culminating in a hyperthermic toxidrome.^{40–42} Features of serotonin syndrome range from those that are barely detectable to those which threaten life. Adding to this diagnostic difficulty, there is evidence that 85% of physicians are not aware of serotonin syndrome as a diagnostic entity.⁴³ It is of relevance to patients at the end of life, as medications commonly used to control symptoms, including some opiate analgesics, have been implicated in its pathogenesis.⁴⁴ In addition, early features of serotonin syndrome may be wrongly attributed to other causes and inadvertently treated with medications likely to exacerbate the patient's condition.⁴⁵

Incidence

A rise in the witnessed incidence of serotonin syndrome is felt to be the result of increased prescribing of serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs).⁴⁶ The true incidence of serotonin syndrome is unknown with reports consisting of case studies or post-marketing surveillance data from serotonergic drugs.^{47 48}

Clinical features

Serotonin syndrome is considered a continuum of symptoms progressing from mild side effects to toxicity.⁴¹ It has been described as a clinical triad of neuro-excitatory features including mental status changes, autonomic hyperactivity and neuromuscular abnormalities.^{47 49} Three levels of severity of symptoms and signs have been described:

1. Mild state of serotonin related symptoms
2. Serotonin syndrome
3. Serotonin toxicity

In the presence of features suggestive of serotonin syndrome, the diagnosis can only be made when a patient has a history of serotonergic drug use. Differential diagnoses include neuroleptic malignant syndrome (NMS) and anticholinergic syndrome.^{42 50} Diagnosis has been historically guided by Sternbach's criteria which have been revised by Radomski in 2000 (box 3).^{51 52}

Box 2: DSM-IV-TR research criteria for neuroleptic induced acute akathisia

- A. The development of subjective complaints of restlessness after exposure to a neuroleptic medication.
- B. At least one of the following is observed:
  - fidgety movements or swinging of the legs
  - rocking from foot to foot while standing
  - pacing to relieve restlessness
  - inability to sit or stand still for at least several minutes
- C. The onset of symptoms in criteria A and B occurs within 4 weeks of initiating or increasing the dose of the neuroleptic, or of reducing the medication used to treat (or prevent) acute extrapyramidal symptoms—for example, anticholinergics.
- D. The symptoms in criterion A are not better accounted for by a mental disorder (for example, schizophrenia, substance withdrawal, or agitation from a major depressive or manic episode). Evidence that symptoms may be better accounted for by a mental disorder include the following: the onset of symptoms preceding the exposure to the neuroleptic, the absence of increasing restlessness with increasing doses, and the absence of relief with pharmacological intervention.
- E. The symptoms in criterion A are not due to a non-neuroleptic substance or to a neurological or other general medical condition.³⁷

Box 3: Sternbach's criteria

- Mental (cognitive and behavioural) status changes
  - major symptoms: confusion, elevated mood, coma
  - minor symptoms: agitation, nervous and insomnia
- Autonomic symptoms
  - major symptoms: fever, hyperhidrosis
  - minor symptoms: tachycardia, tachypnoea, dyspnoea, diarrhoea, hypotension, hypertension
- Neurological symptoms
  - major symptoms: myoclonus, tremors, chills, rigidity, hyperreflexia
  - minor symptoms: impaired coordination, mydriasis, akathisia

The onset of serotonin syndrome is usually rapid, often taking place within hours of serotonergic medication ingestion.^{40–53} Initially the patient is alert with tremor and hyperreflexia. Mental status changes are present in 40% of recorded cases.^{40–42–47–54} Neuromuscular signs are initially greater in the limbs. Autonomic features then follow but do not normally cause a management problem. Rigidity and temperature of over 38°C indicate life threatening toxicity.⁴⁹

Pathogenesis

Drugs that elevate brain and spinal cord serotonin levels are capable of causing serotonin syndrome. Overdoses of serotonin reuptake inhibitors frequently produce pronounced serotonergic side effects and in 15% of cases moderate serotonin syndrome.⁴⁹ There is clear evidence supporting a dose–effect relationship.⁵⁵ Combinations of serotonergic drugs acting by different mechanisms are capable of producing life threatening serotonin syndrome.⁴⁹

The increase in SSRI prescribing seen in recent years is also evident in palliative care. This probably reflects an intention to avoid side effects posed by older antidepressants such as tricyclics. This trend, however, appears to correlate with an increasing incidence of serotonin syndrome.⁴⁶ Patients with palliative care needs may already have elevated serotonin levels⁴⁵ as endothelial damage resulting from severe illness can lead to reduced serotonin breakdown by monoamine oxidase activity.

Drug causes

Some opiate analgesics cause serotonin reuptake inhibition. In particular, pethidine, tramadol, fentanyl and dextromethorphan, when co-prescribed with monoamine oxidase inhibitors (MAOIs), have been implicated in fatalities from serotonin syndrome.^{40–41–44} Morphine, codeine, oxycodone and buprenorphine by comparison have been shown not to inhibit serotonin reuptake and therefore are not implicated in serotonin syndrome.⁴⁹

Tricyclic antidepressants (TCAs) are used commonly for the treatment of neuropathic pain in a palliative setting. There is uncertainty as to which TCAs cause clinically significant rises in serotonin levels. Clomipramine exerts a notable serotonergic effect whereas amitriptyline does not.^{55–56} 5HT₃ antagonists such as ondansetron may have a role in the development of serotonin syndrome, but this is still uncertain.⁵⁷

Metoclopramide has been shown to cause serotonin syndrome when prescribed alongside SSRIs.⁵⁸ Cyclizine and haloperidol have been implicated in mild serotonin syndrome, but their ability to cause significant toxicity is uncertain. Atypical antipsychotics, including risperidone, can result in significant serotonin syndrome, particularly when used in combination with SSRIs.⁵⁹

Treatment

If serotonin syndrome is suspected, serotonergic drugs should be discontinued and no other precipitants administered.^{48–50} Rapid resolution of features, usually within 24 h, is seen in many cases upon cessation of the causative agent and supportive care.^{40–42} Some patients may have features persisting beyond 24 h, symptom duration being influenced by the half life of the causative drug.⁵⁰

In addition to supportive care there may be a role for pharmacological therapy in the treatment of serotonin syndrome.⁵³ The intensity of intervention depends on the severity

of toxicity. For mild cases, supportive management may include intravenous fluids and the administration of benzodiazepines. Some authors claim the control of agitation (for all levels of severity) by benzodiazepines is essential in the management of serotonin toxicity.⁴⁷ Serotonin receptor antagonists may be administered. The effective use of cyproheptadine in the management of serotonin syndrome has been reported, although further evaluation is needed. Chlorpromazine has been used in patients with severe toxicity.⁵⁵ Severe serotonin syndrome may be life threatening, particularly if MAOIs or SSRIs are co-ingested, and as such, early hospitalisation is recommended.⁴⁹ In cases of severe toxicity, external cooling, muscular paralysis with neuromuscular blocking agents, mechanical ventilation and intravenous sedation in an intensive care unit are indicated.⁴⁶

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome (NMS) is a rare but potentially lethal adverse reaction arising from the use of medications that involve the central dopaminergic system⁶⁰ such as phenothiazines, butyrophenones and the more recent atypical agents.^{61–63}

Incidence and cause

Several prospective studies from psychiatric settings have reported a prevalence of NMS ranging from 0.07–2.2% of patients receiving neuroleptics.⁶⁴ It has been reported most commonly with haloperidol and depot agents used in psychiatry. It has also been reported with lithium, carbamazepine, desipramine, dothiepin and other neuroleptics.^{65–66}

In the context of palliative care, NMS has been reported with use of metoclopramide and its withdrawal,^{61–69} with levomepromazine, paroxetine and with the abrupt withdrawal of anticholinergic drugs.^{70–73}

Key references

Delirium

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Drug induced parkinsonism

- ▶ Caligiuri MR, Jeste DV, Lacro JP. Antipsychotic-induced movement disorders in the elderly: epidemiology and treatment recommendations. *Drugs Aging* 2000;**17**:363–84.

Akathisia

- ▶ White C, Jackson N. Acute akathisia in palliative care. *Eur J Palliat Care* 2005;**12**:5–7.

Serotonin syndrome

- ▶ Anderson T, Watson MS, Marr K. Serotonin syndrome: a hidden danger in palliative care. *Eur J Palliat Care* 2005;**12**:97–100.

Neuroleptic malignant syndrome

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Clinical features

NMS is characterised by altered levels of consciousness, extrapyramidal effects (rigidity and akinesia), autonomic instability, hyperthermia, sweating and tremors or rigors.^{74–76} Muscle rigidity is the cardinal feature of NMS and is often associated with myonecrosis, myoglobinuria, and elevated serum creatinine phosphokinase (CPK) levels.⁷⁷ Rigidity may be accompanied by tremor, oro-bucco-lingual dyskinesias and sometimes by dysphagia and dysarthria. Leucocytosis is frequently a feature. The symptoms and signs can occur very rapidly or over several days after commencement of a neuroleptic. Sialorrhoea, tachycardia, hyperventilation and labile blood pressure can also occur.⁷⁸ The associated cerebral disturbance can present as confusion, delirium, stupor or coma.^{64 79}

With altered levels of consciousness, dehydration is common. This, combined with rhabdomyolysis, can lead to acute renal failure, one of the more serious complication of NMS.⁷⁴ Death has been reported to occur in 20–40% of cases.^{75 80 81}

Management

The following treatment algorithm has been suggested for NMS⁸²:

1. An immediate withdrawal of all neuroleptic medication as soon as the condition is suspected.
2. Evaluate the patient's fluid balance and hydrate accordingly.
3. If signs persist or worsen after the previous two steps, consider adding a minor tranquilliser such as lorazepam or diazepam.
4. If signs persist or worsen after step 3 consider adding bromocriptine or dantrolene. Dantrolene has been suggested where muscle tone is prominent; bromocriptine is suggested for cases with prominent mental status changes.

Neuroleptics should be used with caution in a patient with a previous history of NMS. Prevalence of recurrence of NMS with re-introduction of neuroleptic has been reported as 25–75%.

CONCLUSION

Drugs commonly used for symptom control in palliative care can give rise to a wide range of neuropsychiatric phenomena. Delirium is frequently seen, akathisia and drug induced parkinsonism are less common, and serotonin syndrome and neuroleptic malignant syndrome are rare but can be fatal when missed. This article aims to raise awareness of drug related neuropsychiatric complications, to aid their detection and appropriate management, and thus improve symptom control at the end of life.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. Akathisia:

- (A) Akathisia is a condition characterised by objective motor agitation and subjective inner restlessness
- (B) Akathisia is most commonly observed in patients taking neuroleptic drugs but can also occur with other non-neuroleptic medications such as prochlorperazine
- (C) Dose and rate of increment of dose are not thought to play a role in the development of akathisia
- (D) The symptoms of this condition are usually observed hours after administration of the causative drug

- (E) The DSM IV research criteria for neuroleptic induced akathisia can be useful in the diagnosis of akathisia caused by other drugs

2. Drug induced parkinsonism (DIP):

- (A) Signs of DIP take several months to become evident
- (B) In DIP tremor and rigidity are the first clinical signs to emerge
- (C) Dopamine receptor occupancy of up to 70% will cause DIP
- (D) Atypical neuroleptics are less likely to cause DIP than drugs like haloperidol
- (E) DIP is recognised in less than 20% of patients taking neuroleptics

3. Neuroleptic malignant syndrome (NMS):

- (A) NMS can present clinically as a delirium
- (B) NMS can cause renal failure
- (C) Measurement of creatinine phosphokinase (CPK) levels are necessary if NMS is suspected
- (D) Any psychoactive medication can give rise to NMS
- (E) If NMS is suspected, anticholinergic medication should immediately be administered

4. In serotonin toxicity:

- (A) Use of a serotonergic agent is necessary to make the diagnosis
- (B) Only patients demonstrating neuro-excitatory, autonomic and neuromuscular features can be diagnosed with this condition
- (C) Patients with palliative care needs may already have elevated serotonin levels
- (D) Combinations of serotonergic drugs acting by different mechanisms are generally safe
- (E) Initial treatment includes immediate discontinuation of serotonergic medication

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ANSWERS

1. (A) T (B) T (C) F (D) F (E) T
2. (A) F (B) F (C) F (D) T (E) F
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