

The Appropriate Use of Antipsychotic Medications in Older People

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Abstract

This clinical review seeks to clarify the appropriate use of antipsychotics in the elderly and provide evidence-based good practice prescribing guide for clinicians. By reducing inappropriate prescribing we reduce harm and improving the safety of older people. Also, reducing the number of older people with psychosis and /or dementia who are receiving inappropriate anti-psychotic medication will have economic impact by reducing the risk of side-effects, death and stroke. Finally, we need to improve service provision through better joint-working and communication across health, social care, the third sector and other agencies.

Keywords: Dementia, Psychosis, Older people, appropriate Medications, Prescribing

INTRODUCTION

Among elderly patients, psychotic symptoms can be seen in a wide range of conditions. The causes and clinical manifestations of the symptoms will vary with the underlying condition. In older people psychotic symptoms of acute onset are usually seen in delirium secondary to a medical condition, drug misuse and drug-induced psychosis. Chronic and persistent psychotic symptoms may be due to a primary psychotic disorder (chronic schizophrenia, late-onset schizophrenia, delusional disorders, and affective disorders), psychosis owing to neurodegenerative disorders (Alzheimer's disease, vascular dementia, dementia with Lewy bodies and Parkinson's disease) or chronic medical conditions. Psychotic symptoms can be associated with aggressive or disruptive behaviour and are often a source of distress to caregivers. They can result in neglect and abuse of elderly patients and persistent symptoms often result in institutionalization, which imposes a heavy financial burden (Karim, & Byrne, 2005).

According to Martindale, and Summers (2013) psychosis is commonly described as a mental state in which there is an altered relation to reality. Usually, reality is taken to mean external reality. However, in

psychodynamic approaches to all mental phenomena there is emphasis not only on impressions of external reality but also on changes in processing of psychic or internal emotional reality. These changes help the mind create a more acceptable view of itself and its intersubjective reality, and are mostly in broad accordance with the views of others (these are the defence mechanisms of the non-psychotic part of the personality). Sometimes, however, the mind creates a new 'reality' that is more acceptable to it but which is outside the sphere of 'common sense' (this is the functioning of a psychotic part of the personality).

This paper seeks to clarify the issues and suggest good practice for old age psychiatrists.

BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS (BPSD) IN DEMENTIA

BPSD are common in dementia and occur in about 90% of individuals with dementia at some points in their illness, (frequency increases with severity of dementia), causing considerable distress and/or risk of harm to the individual, increasing distress to the family/carer and potentially interfering with/preventing the provision of required care. These behaviours are the result of a complex interaction between the illness, the environment, physical health,

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medication and interactions with others. These symptoms can often remit spontaneously, but they can also be persistent and severe.

The presenting neuropsychiatric symptoms include restlessness, wandering, agitation, aggression, sleep disturbance, sexual disinhibition and shouting are collectively referred to as 'behavioural and psychological symptoms of dementia' (BPSD). The variety of symptoms each needs to be treated specifically. More than one symptom can occur at the same time and the clinician needs to decide which symptoms need to be tackled first and by what approach. This diverse range of symptoms often is reported as a single primary outcome measure in clinical trials. As a result, the efficacy of therapies for specific symptoms can be difficult to determine. Clinically, the key symptoms are aggression, agitation, psychosis, and mood disorders. Symptoms that do not usually respond to antipsychotics include wandering, social withdrawal, shouting, pacing, touching, cognitive defects and incontinence.

The management of BPSD is based on a person-centred approach to care, which sees the person first and the dementia second. In making a formulation the clinician needs to see the world from the person's perspective and responds to both their immediate needs and includes an understanding of their deeper unmet psychological needs.

Non-pharmacological therapies include: behavioural therapy, reality orientation, validation therapy, reminiscence therapy, complementary therapy, art, therapy, music therapy, activity therapy, aromatherapy, bright-light therapy, multisensory approaches, cognitive behavioural therapy and interpersonal therapy. Best evidence available is for Cognitive Stimulation, Behavioural Management Techniques, Snoezelen and Music therapy. Other useful techniques include manipulating the environment, training for resolution of aberrant behaviour, providing cues and structured activities.

For environmental cause or disturbing events, staff can consider non-pharmacological approaches such as: distraction, leave & return, activity, one-to-one care, music, aromatherapy. Reassure in advance of event(s) and maintain calm, stable environment.

For people with a diagnosis of dementia, behaviours that challenge are best 'managed' by good nursing care,

the correct environment and use of 'ABC' (antecedents, behaviours and consequences) to try and identify causes and possible triggers for the presenting behaviour. Also, the use of FITS (Focused Intervention Training and Support) should be considered. Initial treatment should focus on ruling out or treatment of differential diagnoses. Examples that can cause behavioural symptoms include delirium, constipation, pain (even without overt symptoms), infection, activity related, side-effects of medication, or environmental factors. Where functional mental health problems exist e.g. depression, anxiety, insomnia or psychosis these should be treated according to local guidelines. Non-pharmacological treatments should be considered first line. Non-pharmacological and pharmacological treatments should not be seen as separate and used in combination where appropriate.

Pharmacological Intervention for BPSD

There is no drug licensed specifically for 'BPSD', but there are some BPSD symptoms for which there are licensed indications (e.g. depression or psychosis). Drug treatments for all other BPSD symptoms are therefore 'Off License'. Anti-dementia drugs do have a beneficial effect on some behavioural symptoms of dementia though the benefits have so far been shown in people with milder behavioural problems and it takes some a few weeks for their effect to be manifest (Tariot et al, 2001; McKeith et al, 2000).

Whatever the severity and urgency of the situation, it is vital that the doctor assesses the situation as fully as practically possible by speaking to the patient and informants and then decides the best balance of risks and benefits for the patient of every possible treatment. If the patient has capacity to understand these risks and benefits of treatment approaches then consent to treatment should be sought. If the patient does not have capacity to consent to treatment then these risks and benefits should, where practical, be discussed and communicated to the General Practitioner, relatives and carers. Ultimately the doctor has the responsibility for the decision to implement treatment. Relatives cannot consent on behalf of their incapacitated relatives.

For drug treatments the '3T' approach is good practice: drug treatments should have a specific target symptom, the starting dose should be low and then titrated upwards and drug treatments should be time limited.

ANTIPSYCHOTIC DRUGS AND TREATMENT OF SPECIFIC SYMPTOMS

- A number of trials showed that antipsychotics prescribed to control BPSD were largely ineffective, and did considerable harm, causing serious physical side effects, increasing the risk of stroke and premature death, and potentially making the symptoms of dementia worse (Ballard et al., 2009). These findings were considered by an All Party Parliamentary Group inquiry into the prescription of antipsychotic drugs to people with dementia living in care homes. The 2008 report recommended that the National Dementia Strategy for England include an action plan to reduce the number of prescriptions for antipsychotics, and that care home staff should be trained to support people with BPSD without using medication. A further report by Professor Sube Banerjee (2009) concluded that two-thirds of antipsychotic prescriptions for dementia were inappropriate. NICE now recommends not using medication to manage BPSD unless people are severely agitated. The National dementia strategy for both Wales and Scotland also has similar recommendations.
- The atypical antipsychotics Risperidone and Olanzapine have the best evidence base for effectiveness compared to placebo for physical aggression, agitation and psychosis. The effect of atypical antipsychotics in these situations is not entirely attributable to sedation. Typical antipsychotics are effective with similar symptoms but have a weaker evidence base
- Similar types of side-effects can occur with all antipsychotics but the severity and frequency of each side effects is different in the two groups. At effective doses typical antipsychotics tend to have more side effects which are more severe . Typical antipsychotic side effects are more likely to include extrapyramidal side effects, tardive dyskinesia, anticholinergic side effects (with possible acceleration of cognitive decline) and drowsiness (in higher doses). At their usual doses atypical antipsychotic side effects are more likely to include weight gain, disrupt blood glucose control, hyperlipidaemia and CVAEs. At higher doses sedation and extrapyramidal side effects can occur as well.
- Both classes of drugs can cause paradoxical agitation. The choice between the two classes of drugs should be informed by these general side effect profiles as well as any the individual circumstances of the case.
- A decision to start atypical antipsychotic drugs should be adequately documented. A clear date to review the need for these drugs should also be noted.
- The NICE/SCIE guideline on dementia recommends that people with dementia who develop non-cognitive symptoms that cause them significant distress or who develop behaviour that challenges should be offered an assessment at an early opportunity to establish likely factors that may generate, aggravate or improve such behaviour. The assessment should be comprehensive and include for example, the person's physical health, depression, undetected pain or discomfort, side effects of medication, psychosocial factors, physical environment factors, and the person's religious beliefs and spiritual and cultural identity. Individually tailored care plans that help carers and staff address the behaviour that challenges should be developed, recorded in the notes and reviewed regularly.
- For people with all types and severities of dementia who have comorbid agitation, the NICE/SCIE guideline on dementia recommends that non-pharmacological approaches may be considered including aromatherapy, multisensory stimulation, therapeutic use of music or dancing, animal assisted therapy, and massage.
- The NICE/SCIE guideline on dementia advises against the use of any antipsychotics for noncognitive symptoms or challenging behaviour of dementia unless the person is severely distressed or there is an immediate risk of harm to them or others.
- Any use of antipsychotics should include a full discussion with the person and carers about the possible benefits and risks of treatment.
- Review and, if appropriate, optimise prescribing of low-dose antipsychotics in people with dementia, in accordance with the NICE/Social Care Institute for Excellence (SCIE) guideline on dementia and the NICE quality standard on dementia.

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- For prescribers considering using antipsychotics in people without a current prescription: Carefully consider, after a thorough clinical examination including an assessment for possible psychotic features (such as delusions and hallucinations), whether a prescription for an antipsychotic drug is appropriate.
- For prescribers considering continuing antipsychotics in people with a current prescription: Identify and review people who have dementia and are on antipsychotics, with the purpose of understanding why antipsychotics have been prescribed.
- In consultation with the person, their family and carers, and clinical specialist colleagues such as those in psychiatry, establish: whether the continued use of antipsychotics is appropriate; whether it is safe to begin the process of discontinuing their use; and what access to alternative interventions is available.
- Psychotropic medications such as neuroleptics and benzodiazepines should be started at the lowest possible dose and should be used for shortest duration.
- Where the target symptoms undergo remission, then there has to be a review of need for medication. Trial without medication may be offered where appropriate to avoid adverse effects from long-term use of medications.
- CMHTs can be contacted for specialist advice about changing doses or discontinuing medications used for managing BPSD.
- For agitated dementia with delusions, the first-line recommendation is an antipsychotic drug alone; also, adding a mood stabilizer can be considered. Risperidone (0.5-2.0 mg/day) was first line followed by quetiapine (50-150 mg/day) and olanzapine (5.0-7.5 mg/day) as high second-line options.

ALTERNATIVE MEDICATIONS TO ANTIPSYCHOTIC USE

Antidepressants for Depression, Agitation and Psychosis in Dementia

- Depression is common in people with dementia and many patients are prescribed antidepressants. Current evidence offers only weak support for this practice. However, this conclusion is based on a very small number of studies with small

sample sizes, predominately investigating classes of antidepressants not routinely used in clinical practice. Perhaps the main value of this review is to draw attention to this issue. It is not that antidepressants are necessarily ineffective but rather that there is not much evidence to support their efficacy. Given that they may produce serious side-effects clinicians should therefore prescribe with due caution.

- Psychosis and agitation frequently occur in older adults with dementia. Medications are often prescribed to treat these symptoms and antidepressants are increasingly used for these symptoms. We reviewed the evidence for the effectiveness and safety of antidepressants for the treatment of agitation and psychosis in older adults with dementia. We classified antidepressants based on their mechanism of action and included studies that compared antidepressants to treatment with either placebo or other medications frequently used to manage these symptoms. A total of nine studies (including 692 individuals) were identified, four comparing selective serotonin reuptake inhibitors (SSRIs) to placebo, three comparing SSRIs to typical antipsychotics, and one study comparing SSRIs to atypical antipsychotics. One study compared the antidepressant trazodone to placebo, and two compared trazodone to haloperidol. Most of the studies included in the review were relatively small and of uncertain risk of bias due to methodological issues. The SSRIs sertraline and citalopram were associated with a modest reduction in symptoms of agitation and psychosis when compared to placebo in two studies. There were few other statistically significant differences in changes in agitation or psychosis or in most measures of medication tolerability for SSRIs or trazodone when compared to placebo or the antipsychotic haloperidol. We conclude that there is some evidence to support the use of certain antidepressants for agitation and psychosis in dementia and further studies are required to determine the effectiveness and safety of SSRIs and trazodone in managing these symptoms.

Carbamazepine and Valproate for Treatment of Agitation in People with Dementia

- Carbamazepine has been reported to decrease agitation, impulsivity, and lability in psychiatric illness. These symptoms may be related to kindling phenomena occurring in the limbic system and

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temporal lobes. Kindling represents a process by which increasing behavioural and convulsive responses occur to repetition of the same stimulus over time. Carbamazepine's psychotropic activity may be related to its stabilising effect on kindling phenomena of the amygdala and other limbic structures. Another purported mechanism through which carbamazepine may exert its anti-agitation effect is via the modulation of serotonin transmission.

- An updated review (October 2008) of valproate treatment of agitation in demented patients failed to show any improvement in agitation among treated patients compared with those not receiving treatment, and also demonstrated a higher rate of harmful effects, such as falls, infections and gastrointestinal disorders (diarrhoea, nausea) among those receiving valproate preparations. Although further research on the value of valproate preparations is indicated, current evidence does not support use of this drug to control agitation of people with dementia.

Benzodiazepines Use In Dementia

- The benzodiazepine anxiolytics have been shown to be of some benefit, but all share the side effects of sedation, motor and cognitive impairment, and a propensity to cause withdrawal symptoms when discontinued. Delirium, paradoxical excitation, and falls may also occur.
- Sleep architecture is also altered, with inhibition of both rapid eye-movement (REM) sleep and delta wave sleep. These side effects make benzodiazepines a poor choice for regular use in patients with dementia. They are best used for short-term management of sleep-cycle disturbances or anxiety states, or as planned premedication prior to predictably anxiety-provoking situations.
- As pre-medication prior to frightening situations such as dental or podiatry care, intermediate-acting benzodiazepines can be used on occasion. This is the best use of benzodiazepines for BPSD.

Cholinesterase Inhibitors and Memantine

- Alzheimer's disease and many other forms of dementia are associated with a prominent deficiency of acetylcholine. Cholinesterase

inhibitors increase the residual acetylcholine in the brain and are indicated for treatment of cognitive impairment in patients with mild and moderate AD. The initial studies of cholinesterase inhibitors examined cognitive rather than behavioural end-points. Subsequent studies have shown benefit on cognition in severe AD, other dementias (DLB, VaD), and on behaviours particularly apathy, depression and anxiety.

- A randomized trial of donepezil in nursing home patients with behavioural problems was negative for benefit for the behavioural symptoms while a trial of donepezil in community-dwelling patients with moderate-severe AD was positive for some BPSD, especially in those without concomitant psychoactive medications. A trial of rivastigmine in dementia with Lewy bodies patients showed reduction of apathy, anxiety, delusions and hallucinations. Trials of galantamine in AD have also shown significant benefit for behavioural parameters. These effects on behaviour are in addition to the well-documented benefits in cognitive function with agents such as donepezil, rivastigmine, and galantamine. Their cognitive effects can justify the use of any one of these agents. In situations where the decision to use such an agent is "on the borderline," the potential for a beneficial effect on BPSD can be a factor for consideration.
- It should also be recognized that the headache and others that a dementia patient may find difficult or impossible to describe. If deterioration of behaviour is seen after starting one of these drugs, try stopping the cholinesterase inhibitor and re-evaluating— it may be causing agitation as a response to drug side effects that cannot otherwise be detected.
- Memantine, a non-competitive NMDA glutamate receptor antagonist, has been available in Germany for about 20 years for the treatment of organic brain disease. The drug has recently been approved in Europe and Australia for the management of cognitive impairment in moderately severe and severe AD and is being considered by the regulatory authorities in the United States for the same indication. Studies have suggested less emergent agitation with memantine.

Estrogens and Anti-Androgen Treatments

- Oestrogens and anti-androgen treatment (e.g. medroxyprogesterone acetate and cyproterone acetate) have been proposed for the specific BPSD of sexually inappropriate behaviour or extremely aggressive behaviour in men. Evidence for their use remains anecdotal and there are many potential side effects. In general, they are used as a last resort. Legal restrictions to their use apply in some jurisdictions.

Antihistamines

- Sedating and anticholinergic antihistamines such as diphenhydramine can result in worsening confusion and other symptoms of delirium. They may be perceived inappropriately as safer than “traditional” psychotropic drugs because they are available without prescription in many countries. In general, they are a very poor choice for managing BPSD.

Pain Relief

- Pain is a common medical condition in older persons. Untreated or under-treated pain can produce significant suffering as well as agitation and behavioural problems in persons with dementia. The symptoms of pain expressed by patients with moderate to severe dementia include anxiety, agitation, screaming, hostility, wandering, aggression, failure to eat, and failure to get out of bed. A small number of demented individuals with serious injury may not complain of pain, e.g., hip fractures, ruptured appendix, etc.
- Assessment of pain in the demented patient requires verbal questioning and direct observation to assess for behaviours that suggest pain. Standardized pain assessment scales should be used for all patients; however, these clinical instruments may not be valid in persons with dementia or psychosis. The past medical history may be valuable in assessing the demented resident. Individuals with chronic pain prior to the onset of dementia usually experience similar pain when demented, e.g., compression fractures, angina, neuropathy, etc. These individuals can be monitored carefully and non-narcotic pain medication can be prescribed as indicated, e.g., acetaminophen on a regular basis, anticonvulsants for neuropathy.

- Management of chronic pain involves three elements (1) physical interventions, (2) psychological interventions, (3) pharmacological interventions. Physical interventions include basic physiotherapy that incorporates warm or cool compresses, massage, repositioning, electrical stimulation and many other treatments. Dementia patients need constant reminders to comply with physical treatments e.g., using compresses, sustaining proper positioning, etc., and many do not cooperate with some interventions, like nerve stimulators or acupuncture.
- Physical interventions are particularly helpful in older persons with musculoskeletal pain regardless of cognitive status. Psychological interventions usually require intact cognitive function e.g., relaxation therapy, self-hypnosis, etc.
- Demented patients generally lack the capacity to utilize psychological interventions; however, management teams should provide emotional support to validate the patient’s suffering associated with pain. Demented patients may experience more suffering from pain than intellectually intact individuals because they lack the capacity to understand the cause of their discomfort. Fear, anxiety, and depression frequently intensify pain.
- Pharmacological management begins with the least toxic medications and follows a slow progressive titration until pain symptoms are controlled. The goal of pain management is to remove the suffering associated with the painful stimulus rather than making the patient euphoric or high to the point where they no longer care whether they experience pain. Euphoria-producing medications can cause confusion, irritability, and behavioural lability in patients with dementia. Narcotic addiction is not a common concern in dementia patients as these individuals have a limited life expectancy and rarely demonstrate drug-seeking behaviours.
- A regular dose of paracetamol up to 4 grams per day will substantially diminish most pain and improve quality of life. Clinical studies show that regular Tylenol reduced agitation in over half the treated patients.

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- Chronic arthritic pain with inflammation of the joints may also respond to non-steroidal anti-inflammatory (NSAID) or Cox-2 inhibitors. The gastrointestinal toxicity associated with NSAIDs is greater than that of Cox 2 inhibitor medications. Patients who fail to respond to non-narcotic analgesics should receive narcotic-like medications, i.e., tramadol. Patients who fail to respond to maximum doses of tramadol, i.e., 300 mgs per day, may require narcotic medications.
- For severe nonpsychotic mania, a mood stabilizer is recommended alone; the also consider discontinuing an antidepressant if the patient is receiving one. For severe nonpsychotic mania, a mood stabilizer plus an antipsychotic (57%; first line) or a mood stabilizer alone (48%; first line) and discontinue any antidepressant the patient is receiving.

Antipsychotic Use For Other Psychotic Disorders in the Elderly

- Antipsychotics should not be used in panic disorder, generalized anxiety disorder, non-psychotic major depression, hypochondriasis, neuropathic pain, severe nausea, motion sickness, or irritability, hostility, and sleep disturbance in the absence of a major psychiatric syndrome.
- First-line recommendation for late-life schizophrenia was risperidone (1.25-3.5 mg/day). Quetiapine (100-300 mg/day), olanzapine (7.5-15 mg/day), and aripiprazole (15-30 mg/day) were high second line. For older patients with delusional disorder, an antipsychotic was the only treatment recommended.
- For agitated nonpsychotic major depression in an older patient, the first-line recommendation is an antidepressant alone (77% first line); second-line options are an antidepressant plus an antipsychotic, electroconvulsive therapy (ECT), an antidepressant plus a benzodiazepine, and an antidepressant plus a mood stabilizer.
- For nonpsychotic major depression with severe anxiety, use an antidepressant alone and you can also consider adding a benzodiazepine or mood stabilizer to the antidepressant. If an older patient with adequate dosages for adequate duration, there was limited support for adding an atypical antipsychotic to the antidepressant (36% first line after two failed antidepressant trials).
- Treatment of choice for geriatric psychotic major depression is an antipsychotic such as Aripiprazole plus an antidepressant (98% first line), with ECT another first-line option (71% first line).
- For mild geriatric nonpsychotic mania, the first-line recommendation is a mood stabilizer alone; consider discontinuing an antidepressant if the patient is receiving one.
- For psychotic mania, treatment of choice is a mood stabilizer plus an antipsychotic (98%; first line). Risperidone (1.25-3.0 mg/day) and olanzapine (5-15 mg/day) are first-line options in combination with a mood stabilizer for mania with psychosis, with quetiapine (50-250 mg/day) high second line. If a patient has responded well, consider the following duration of treatment before attempting to taper and discontinue the antipsychotic: delirium, 1 week; agitated dementia, taper within 3-6 months to determine the lowest effective maintenance dose; schizophrenia, indefinite treatment at the lowest effective dose; delusional disorder, 6 months-indefinitely at the lowest effective dose; psychotic major depression, 6 months; and mania with psychosis, 3 months.
- For patients with diabetes, dyslipidemia, or obesity, avoid clozapine, olanzapine, and conventional antipsychotics (especially low- and mid-potency). Quetiapine is first line for a patient with Parkinson's disease. Clozapine, ziprasidone, and conventional antipsychotics (especially low- and mid-potency) should be avoided in patients with QTc prolongation or congestive heart failure.
- For patients with cognitive impairment, constipation, diabetes, diabetic neuropathy, dyslipidemia, xerophthalmia, and xerostomia, risperidone is preferred, with quetiapine high second line.
- Avoid the following combination: clozapine + carbamazepine, ziprasidone + tricyclic antidepressant (TCA), and a low-potency conventional antipsychotic + fluoxetine. In combining antidepressants and antipsychotics, be much more cautious with selective serotonin reuptake inhibitors that are more potent inhibitors of the CYP 450 enzymes (i.e., fluoxetine, fluvoxamine, paroxetine) and with nefazodone, TCAs, and monoamine oxidase inhibitors.

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- Extra monitoring should be made when combining any antipsychotic with lithium, carbamazepine, lamotrigine, or valproate (except aripiprazole, risperidone, or a high-potency conventional plus valproate) or with codeine, phenytoin, or tramadol.

CONCLUSION

Behavioural and psychiatric symptoms are complex and require a comprehensive patient assessment. Non-pharmacological approaches can be effective and should be tried first. Pharmacological approaches effective but concerns around safety persist

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