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PRACTICE

CHANGE PAGE

Don't use antipsychotics routinely to treat agitation and aggression in people with dementia

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Change Page aims to alert clinicians to the immediate need for a change in practice to make it consistent with current evidence. The series advisers are Sera Tort, clinical editor, and David Tovey, editor in chief, the Cochrane Library. We welcome any suggestions for future articles (email us at practice@bmj.com).

Behavioural and psychological symptoms of dementia such as agitation and aggression are commonly treated with atypical antipsychotic drugs, which are associated with severe side effects.[1] However, there is increasing evidence of potential harms associated with use of these drugs in people with dementia, and guidelines increasingly recommend restricting their use. In Europe, only risperidone is currently licensed for use in dementia and only for up to six weeks in patients with severe aggression, defined as causing risk or severe distress, which has not responded to other treatments. No antipsychotics are approved for this patient group in the United States. Best practice guidelines, including National Institute for Health and Care Excellence guidelines in the United Kingdom and American Psychiatric Association guidelines in the US, are similar. However, they do not distinguish between individual atypical antipsychotics and recommend a maximum treatment period of 12 weeks, except in exceptional circumstances.[2 3]

The use of these drugs in people with dementia has decreased worldwide in the past decade. For example, a 2012 audit in the UK indicated a 50% reduction in prescriptions, although 16% of people with dementia continued to receive antipsychotic treatment.[1] Use is mostly off-licence, either prescriptions of antipsychotics such as quetiapine, olanzapine, aripiprazole, and haloperidol without a licence indication or the use of risperidone outside the strict licence indication. In addition, prescriptions often exceed the six week period specified in the licence indication for risperidone or the 12 week prescription period recommended in all of the major best practice guidelines, with 62% of people receiving atypical antipsychotics for six months or more.[1]

Although current guidance promotes more judicious use of these drugs, with regular review of prescriptions, the guidelines are difficult to interpret, particularly as thresholds for severity are unclear.

The evidence for change

Modest short term clinical benefit

Systematic reviews have analysed the clinical effectiveness of antipsychotics in people with dementia. These analyses are based on 18 placebo controlled randomised trials, most of which were conducted over a 10-13 week period. However, many of these trials have not been published in full. The best evidence base exists for risperidone, with five fully published good quality randomised controlled trials (RCTs) and a total of 1761 participants.[4 5] In these trials, full data were presented for aggression and psychosis, but the information on non-aggressive symptoms of agitation such as restlessness, wandering, and shouting was incomplete, which may have led to bias. Adverse events were comprehensively reported in all five studies.[5] A meta-analysis reported a significant advantage for risperidone in the treatment of aggression (−0.84 points on the BEHAV-AD rating scale (95% confidence interval −1.28 to 0.40) at a dose of 1 mg and −1.5 points (−2.05 to −0.95) at 2 mg).[4] This threshold of change indicates a statistically significant difference but only borderline clinically meaningful benefit at the 2 mg dose. Evidence of clinically meaningful benefit is restricted to aggression—none was seen for non-aggressive symptoms of agitation.[4 6] Although outside the focus of this paper, effectiveness is even more limited for the treatment of psychosis. Statistically significant benefit but no clinically meaningful benefit was seen only at 1 mg risperidone (BEHAV-AD mean difference −0.14, −0.25 to −0.03).

The evidence for benefit is not equal for all antipsychotics. For example, a meta-analysis of published trials found no evidence that quetiapine confers benefit in the treatment of behavioural and psychological symptoms of dementia.[4]

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The bottom line

- Despite continued use of antipsychotics to treat agitation and aggression in people with dementia, there is limited evidence of clinically meaningful benefit
- The potential harms of antipsychotic use (including increased cerebrovascular events and mortality) outweigh the benefits
- Risperidone is the only recommended antipsychotic, and should be used only in people with dementia who have pre-existing psychotic disorders or severe aggression. It should be prescribed for no more than 12 weeks
- Careful monitoring is the best practice alternative, with evidence that alternative treatments including analgesia and non-drug based approaches provide effective options

Sources and selection criteria

This article is based on an updated review of the literature published in systematic reviews. We searched the electronic databases PubMed, Embase, and the Cochrane Library. We evaluated individual randomised controlled trials from systematic reviews to calculate the specific attributable risk of key adverse events associated with risperidone in people with Alzheimer's disease. Studies were selected according to the quality and robustness of the study design, with a focus on systematic reviews.

The high placebo response rates (45% *v* 55% for risperidone) across all published trials indicate that benefit is often related to general benefits of good clinical practice, clinical review, treatment of comorbidity, and improved social interaction as a result of trial involvement.

Adverse effects

The evidence of modest clinical effectiveness must be balanced against the considerable risk of adverse events. A systematic review of 15 RCTs of antipsychotics in people with Alzheimer's disease reported a 1% attributable risk of mortality over 12 weeks of treatment (risk difference 0.01, 0.004 to 0.02; P=0.01). A 12 month double blind RCT examining antipsychotic discontinuation in people with Alzheimer's disease, with follow-up of participants for up to five years, found a significant reduction in mortality associated with discontinuation (hazard ratio 0.58, 0.36 to 0.92), with a risk difference in mortality of 29% after 36 months.[4] A subsequent meta-analysis of all 18 RCTs of atypical antipsychotics for the treatment of behavioural and psychological symptoms of dementia also found a clinically significant acceleration of cognitive decline in people taking antipsychotics (mini-mental state examination mean difference 0.73 points, 0.38 to 1.09; P<0.0001) over 12 weeks.

Reporting of adverse events is most complete for risperidone—full data are not available for other antipsychotics because of the large number of unpublished studies. Of particular concern, meta-analyses have established a threefold increased risk of cerebrovascular events in people with Alzheimer's disease who take risperidone compared with those taking placebo (odds ratio 3.43, 1.60 to 7.32; *Z*=3.18; P=0.001), with a risk difference of 3.1% versus 1.0% in a pooled analysis.[7-12] Another important risk is an increased frequency of extrapyramidal symptoms (risk difference by meta-analysis 0.06, 0.03 to 0.09 over 12 weeks). Peripheral oedema, sedation, prolonged Q-Tc interval, infections, and abnormal gait have also been highlighted as potential problems.[6]

Longer term use and discontinuation

Evidence on the long term use of antipsychotics is emerging. A handful of recent trials have evaluated a range of antipsychotics over periods of six months and longer. Only one RCT directly evaluated the impact of an antipsychotic (quetiapine) on agitation, reporting no benefit compared with placebo over six months.[13] Overall, these studies have reported no benefit or very modest benefit in the treatment of the behavioural and psychological symptoms of dementia over six to 12 months. The exception is one recent trial that compared the impact of withdrawal versus continuation of haloperidol, which indicated ongoing benefit of continuation in people who had initially responded to this treatment.[14] A Cochrane review of nine randomised placebo controlled trials concludes that long term prescriptions of antipsychotics can be discontinued without a detrimental effect on neuropsychiatric symptoms.[15]

Adverse events are also more marked with longer term use, with one RCT reporting 59% mortality compared with 30% in a placebo group after 36 months.[16 17] In another nine month RCT of 421 people with Alzheimer's disease, 18% of patients receiving risperidone withdrew from the trial owing to adverse events compared with 5% of those receiving placebo.[12]

Alternatives to antipsychotics

No direct alternatives to antipsychotics are available for the treatment of aggression or psychosis. Results of initial studies with several compounds including carbamazepine, mirtazapine, and prazosin are encouraging, but there is insufficient evidence to recommend their use in clinical practice.[18] Other compounds with similar chemical actions, such as benzodiazepines (other than mirtazapine) are possible candidates, but no evidence from clinical trials is currently available. A recent RCT of citalopram that built on preliminary studies indicated modest but significant benefit in the treatment of agitation at 30 mg per day, but the impact on prolongation of the Q-Tc interval was considered too great to recommend this as a treatment approach.[19] A trial is currently examining the efficacy and safety of a lower dose.

Pain is a common underlying cause of agitation in dementia, and a recent RCT in 352 patients reported a 17% improvement in agitation after stepped treatment with analgesics, similar to the benefit seen with antipsychotics.[20] Such treatment is not a direct alternative to antipsychotics but plays an important part in managing and preventing agitation, and may reduce the need for antipsychotics.

Although there is a substantial evidence base for non-pharmacological approaches to the treatment of behavioural and psychological symptoms of dementia, a more modest number of studies focus on specific interventions for individual symptoms. A recent systematic review reported significant benefit in four of six RCTs that evaluated personalised activities, such as personalised social interaction and reminiscence therapy (box 1) for the treatment of agitation, with a median overall standardised effect size of 0.46.[21] The standardised effect size is calculated by dividing the mean difference between treatments for an outcome by the standard deviation of that measure across the sample. A standardised effect size of 0.4-0.6 is usually considered to represent a moderate and clinically meaningful benefit. For context, the standardised effect size for risperidone for the treatment of aggression is about 0.2. However, such

studies are usually smaller than trials on drug based interventions, and the comparison is usually with treatment as usual rather than a more specific control intervention. Such a design is likely to lead to a higher apparent effect size. The evidence supports the use of these approaches as an effective set of first line interventions, although their impact on severe intractable symptoms may be more limited. They are not an alternative to drug based treatment, but they are the most appropriate initial course of action and may reduce the need for antipsychotic use.

Barriers to change

The behavioural and psychological symptoms of dementia present a substantial treatment challenge for physicians, particularly with the current lack of a licensed drug based alternative and continuing ambiguity in thresholds for prescribing.

Doctors often experience a considerable pressure to prescribe as a result of the distress that these symptoms cause to individuals, their families, and care staff in residential care settings. This complex challenge requires discussion with staff and family members so that they can air their concerns and to ensure that they fully understand the minimal clinical benefit and possible harms associated with antipsychotic treatment.

Identification of pain is included in best practice guidelines for the management of agitation, but it is rarely applied systematically, probably because of the lack of practical guidance. Furthermore, there is currently limited provision of simple first line evidence based alternatives, such as those outlined in box 1, both by primary care and multidisciplinary specialist teams. Guidelines and training programmes exist, but lack of standardised or specific training may result in interventions that provide monitoring or advice for staff but do not deliver simple evidence based treatments. This may in turn lead to the misperception that non-drug based approaches are ineffective. Training for some of these approaches, such as promoting enjoyable activities, is simple and can be delivered in a half day session.

How should we change our practice?

We propose that—in line with current European licence indications—in patients with severe aggression that have not responded to alternative treatment approaches, risperidone should be used for a maximum of six weeks (box 2). The maximum treatment period could be extended to 12 weeks to be consistent with international best practice guidelines.[2 3] Other antipsychotics should not be prescribed for people with dementia. Exceptions should be made only when the individual has a pre-existing psychotic disorder independent of a diagnosis of dementia.

For most people with dementia, the risk of harm of antipsychotic treatment outweighs the likelihood of benefit. Careful ongoing monitoring and support, without the prescription of antipsychotics, is important because clinical trials show that 40-45% of people will experience clinically meaningful benefit from the generic components of good clinical practice.[4 6]

For people who have already been taking antipsychotics for more than 12 weeks, these drugs should be reviewed and discontinued unless at least two previous attempts at discontinuation have led to severe exacerbation of symptoms. In 70% of people, no worsening of symptoms is seen after withdrawal of antipsychotics.[16] Carers may require support over the first four weeks because of anxiety about worsening of symptoms, and monitoring is recommended for up to three months. When possible it can also be helpful to recommend simple non-drug based interventions such as social interaction (box 1).

Non-drug based treatments and improved pain management provide an appropriate first line treatment for agitation and aggression in many people, although these are not a direct alternative to antipsychotics. Routinely assess for pain in all people experiencing behavioural and psychological symptoms of dementia. If there is any suggestion that pain may be contributing, start a trial of treatment for pain through stepped analgesia, starting with paracetamol in the absence of ongoing analgesia.

A first line approach should also include prompt access to simple effective evidence based non-drug treatments, such as personalised activities with social interaction (box 1). If these approaches do not help, refer the patient to a clinical psychologist to assess whether a short term prescription of an antipsychotic is warranted or whether the risk of prescribing outweighs any benefit. In this case, ongoing psychosocial interventions in combination with close monitoring would be more beneficial.

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Box 1: Non-drug treatments for use as first line approaches for behavioural and psychological symptoms of dementia[21]

The Seattle protocols

A personalised approach to care planning that focuses on increasing physical and cognitive activities. This involves meeting with the patient and family to discuss the patient's interests and hobbies. A care plan can then be developed to ensure that the patient performs at least 60 minutes of enjoyable activities a week that also promote physical activity, such as gardening, gentle movement and balance exercises, or walking. Manuals for the Seattle protocols are available online.

Personalised social interaction

This approach focuses on ensuring that the patient regularly spends time interacting with other people. This involves a detailed assessment of the patient's medical and personal needs as well as ability to communicate, move around, and participate in activities. This is then used to create a tailored social interaction programme involving care staff, family members, friends, and others who are available to spend time with the patient.

Brief psychosocial treatment

This is a simplified version of the personalised social interaction approach above, which can be delivered by a family member. The goal is to provide 10 minutes of social interaction each day, which can involve talking about topics that interest the person (such as asking about past work, family, or hobbies), looking at photographs, or doing a puzzle together. Support is available through an initial 30 minute planning session with a trainer and brief weekly follow-up telephone calls.

Simulated presence therapy

This simple approach uses audio or video recordings from family members, such as recorded conversations, singing, or home videos, which are played to the patient in the care setting. The goal is to simulate social contact and to prompt memories and conversation. The recordings could also be used as part of an enjoyable activity, such as looking through old photographs. This approach works best when working closely with families to agree on the most suitable recordings on the basis of the patient's interests.

NEST approach

This more in-depth approach is suitable for use by an occupational therapist. It involves evaluating patients' needs, and the environment, stimulation, and techniques (NEST) that they require; this is then used to select different activities they can engage in.

Box 2: Current guidelines for use of risperidone in people with behavioural and psychological symptoms of dementia[22]

Risperidone is the only recommended treatment

Maximum length of treatment is 12 weeks

It should be used only in patients with severe aggression that is causing risk or severe distress and where alternative approaches have failed

The decision to prescribe should be made only after a careful risk assessment, particularly cerebrovascular risk (taking into account hypertension, diabetes, smoking, atrial fibrillation, and previous stroke)

Report all suspected side effects to the appropriate regulatory body

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