EDITORIAL

International Journal of Geriatric Psychiatry

Benefit–risk analysis for the clinician: `primum non nocere' revisited—the case for antipsychotics in the treatment of behavioural disturbances in dementia

The results of clinical trials are often presented in a way that only highlights either the benefits or the risks of the treatment under study. Especially in older age, clinical psychiatric problems are often of complex nature, which requires integrating multiple sources of data to reach clinical decisions. An analytical, decision-making strategy can be of help in arranging the results of various studies in such a way as to aid decision-making. In this paper, we clarify this method using the case of the risks and benefits of using antipsychotics in older people with dementia and behavioural disturbances.

Key words: antipsychotics; behaviour; dementia; decision-analysis
History: Received 29 March 2009; Accepted 15 June 2009; Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/gps.2357

Introduction: using antipsychotics for behavioural disturbances in dementia

Douglas and Smeeth presented the results of their study on exposure to antipsychotics and the resulting elevated risk of stroke in BMJ recently (Douglas and Smeeth, 2008). In another study, Ballard also demonstrated that long-term use of antipsychotics increased the mortality risk in older people with dementia and behavioural disturbances (Ballard *et al*., 2009). The quality of this research is good and the outcome is of great importance and interest to clinicians. However, in a letter, Conradi went so far as to call it 'modern madicine', irritated as he was by the fact that his clinical practice was written off without giving any alternatives for the major challenge that behavioural disturbances in dementia can present (Conradi, 2008). This illustrates a common situation in geriatric medicine, in which clinicians are faced with severe and complex pathology, in which intervening carries the risk of causing substantial harm to the patient.

In their paper, Douglas and Smeeth have only given us the intervention and the (negative) outcome. Although there is nothing wrong with that kind of research —as we stated, it is of great importance—it shows just one side of the coin. All medical interventions have their side effects. We think that most doctors will act—as they have sworn—to do as little harm as possible to their patients and therefore easily lose sight of all the possible positive and negative outcomes of their interventions when such horrendous consequences such as a stroke are at stake. On the other hand, there are many medical interventions with apparent risks and even harm that are nevertheless part of common medical practice. For example, a surgeon may be faced with a patient with a diabetic foot and has to decide whether to amputate or not. Obviously, both decisions, amputation or not, will lead to loss of function and probably more or less morbidity. The ultimate decision should depend on a careful weighing of the likelihood and effects of different outcomes, combined with the patient's assessment of these various outcomes.

It strikes us that in general medicine, such an analytical clinical decision-making strategy is a rather accepted approach, but in psychiatry it is still unusual. We feel that an analytical clinical approach to making decisions could be of great value for day-to-day psychiatric practice. In this paper we do not attempt to make a rigorous estimate of all risks and benefits of antipsychotic treatment in patients with dementia, but will show that even a simplified model may lead to a different decision and that 'primum non nocere' can be a difficult task.

Decision analysis

In decision analysis, one aims to create new insight into a clinical problem by structuring the available data (Kapur, 2000). Most of the time, it is in regard to a clinical problem in which there is no single option that is clearly preferred over another, because if that were the case, then further analysis would be superfluous. In

decision analysis a decision tree is made. At every branch of this tree, there will be several options and a choice has to be made between these various options. As a first step, the likelihood of each of these possibilities needs to be estimated as accurately as possible. These likelihoods can be extracted from RCTs, but there are not always RCTs available on the desired clinical questions. In these cases one should try to arrive at a range of probabilities, extracted from experts in the field using a 'best guess' approach. The second step is to estimate the utility or benefit of each branch of the tree (for example the cost and benefit of some diagnostic procedure). As the benefit is called the utility, the cost is referred to as the dis-utility. Utilities are given in a number between 0 and 1, where 0 is the worst possible outcome (i.e. death) and 1 the best (i.e. perfect health). The expected benefit of a treatment or procedure can be calculated by multiplying the probability of the outcome with the utility or dis-utility.

A decision tree should show enough complexity and details to give way to all relevant clinical elements but on the other hand it should also visualize this complexity in a simple manner.

An analytical approach to making decisions regarding antipsychotics in dementia

In the case at hand, the patients of interest are older people with dementia and severe behavioural disturbances. For this example we state that our subject is an 80-year-old man with severe behavioural disturbance and dementia. The clinician considers antipsychotic medication in order to ameliorate the behavioural disturbance. There are several possible outcomes of this intervention. These are shown in Figure 1. The same kind of tree can be drawn up for other therapeutic actions or for 'doing nothing at all'.

For each possible outcome, we should establish both their likelihood of occurring and their corresponding utilities or dis-utilities. To ascertain utilities is arbitrary, but this can be dealt with by performing a sensitivity analysis. For the purpose of this paper we have adopted a (dis)utility of 0.4 for stroke, of 0.9 for other complications (such as Parkinsonism, sedation) and of 0.8 for persisting behavioural disturbances. Population figures on new strokes in 80-year-old male were found in the Dutch website from the RIVM (http://www.rivm.nl/vtv/object_document/o1027n17966.html). Among men in the age-bracket 80–84 the prevalence of stroke is 19.86 per 1000. Assuming that the figures given by Douglas and Smeeth are correct, we can also specify the chances for developing stroke after starting antipsychotics. They state that the use of antipsychotics is associated with a risk ratio of 3.50 in older people with dementia. This means that the prevalence of stroke would increase to a total number of $3.50 \times 19.86 = 69.51/1000$ males.

Next, we have to establish the beneficial effects of antipsychotics with regard to the behavioural disturbances. There are several reports on the subject, but results are conflicting and not easily comparable. A Cochrane review on the use of atypical antipsychotics for aggression and psychosis in Alzheimer's disease concludes that both risperidone and olanzapine are useful in reducing aggression and psychosis (Ballard *et al*., 2008). Most studies report changes in aggressiveness and psychosis on various scales like the Neuropsychiatric Inventory (NPI) and the Cohen Mansfield Aggression Inventory (CMAI). However, for the current analysis we require figures on significant clinical response to antipsychotics in behavioural disturbances in subjects with dementia (Sultzer *et al*., 2008; Schneider *et al*., 2006). Sultzer *et al*. state that around 60% of subjects improve significantly in terms of symptoms of aggressiveness and psychosis after starting antipsychotics (Sultzer *et al*., 2008).

Of all the other complications, we only include psychomotor disturbances (Parkinsonism) in this analysis for the sake of clarity. This adverse effect of antipsychotics is very common and a major problem in the (very) old and even more so in older people with dementia. We think it is fair to state that around 70% of subjects will suffer from these side effects in a significant way, affecting quality of life and producing additional risks like falls and subsequent fractures, although the latter effects appear in only a minority of subjects. Furthermore, risk of falls is also present in the untreated group, because of behavioural disturbance and distress. We therefore have left out falls and fractures in our further analysis.

An integrated model with all branches of the tree

We can now calculate the results of the various options (branches of the tree).

Option one: no treatment at all

This will give rise to a stroke in 2% of subjects and persistent behavioural disturbances in most of the others, for this example set at 90%. In 8% thus, the

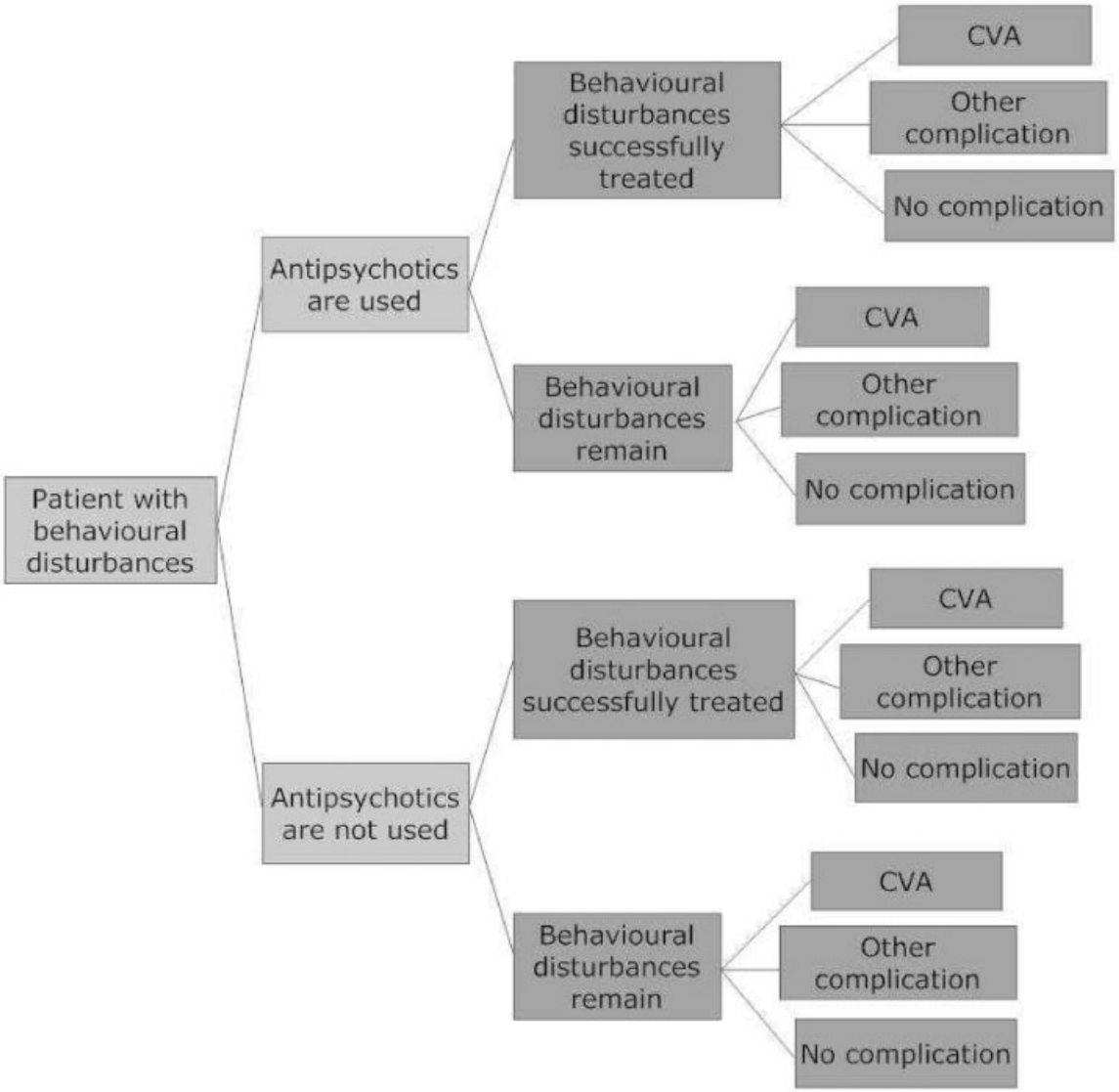

Figure 1 Decision tree.

symptoms will disappear without treatment. Thus, the calculated utility in this group will be: $0.02 \times 0.4 + 0.90 \times 0.8 + 0.08 \times 1 = 0.808$.

Option two: treatment with antipsychotics

This will give rise to a stroke in 7% of subjects. Persistent behavioural disturbances will be present in 40% of the remaining subjects. Of the remaining subjects, 70% will improve with regard to their behavioural disturbances but suffer from motor side effects, i.e. 37% of the total group and finally 16% will improve without major side effects. Thus, the calculated utility in this group will be: $0.07 \times 0.4 + 0.40 \times 0.8 + 0.37 \times 0.9 + 0.16 \times 1 = 0.841$.

Discussion

As we argued in our introduction, when confronted with complex clinical decisions, doctors often stick to the precept: 'primum non nocere'. There is no doubt about the value of this principle, but sometimes doctors lose sight of the pros and cons of their actions, especially when potential side effects of those actions are rather dramatic. With the use of antipsychotics in older people with dementia a dramatic side effect has

been reported: subjects have a 3.5 times higher risk of suffering a stroke.

However, doctors should also be aware of the side effects of not intervening at all. This is the point where clinical decision-making comes at play. Knowledge of various risks and values and also patient appraisal of these various outcomes is of major importance before one decides to intervene or not with a specific treatment. Such evaluations should become more routinely applied in psychiatric practice. Other examples from clinical practice that could be discussed in a similar way are (a) the use of antidepressants (ssris) in adolescents and the risk of suicide or (b) the occurrence of a metabolic syndrome with chronic (successful) use of antipsychotics.

In our example we have estimated the dis-utility for subjects suffering a stroke to be twice as severe as those suffering persistent behavioural disturbances. As we have stated, this is a rather arbitrary choice. Would we have estimated the chance of suffering stroke as four times worse than suffering persistent behavioural disturbances and also appraise persistent behavioural disturbances equally worse as the motor side effects, then the outcome of our analysis would be quite different. Not intervening with antipsychotics would thus lead to a calculated utility of $0.02 \times 0.2 + 0.90 \times 0.8 + 0.08 \times 1 = 0.804$, while interventions with antipsychotics would lead to a calculated utility of $0.07 \times 0.2 + 0.40 \times 0.8 + 0.37 \times 0.8 + 0.16 \times 1 = 0.79$. With such an appraisal of various outcomes, one probably would prefer not to intervene with antipsychotics. The likelihood of the outcome is an estimate, which by definition also carries a certain level of uncertainty. The level of confidence surrounding the likelihood of essential outcomes may vary in different clinical decisions. Taking this into account systematically can help to improve clinical decision-making. The key point in this evaluation, however, is the appraisal of the loss and benefit of the different options, which are often difficult to compare. It is vitally important to discuss possible outcomes with individual subjects, because personal or cultural values and beliefs can affect the subjective appraisal of the individual.

In this paper, we did not aim to come to a rigorous estimate of all risks and benefits of antipsychotic treatment in patients with dementia. To come to such an estimate, a holistic approach that includes all available evidence, would be necessary including uncertainty levels of the various outcomes (Holden, 2003). Our paper is also not a call to intervene with antipsychotic medications in patients with behavioural disturbances in dementia, but a call for a thorough evaluation before making a decision.

Key points

- A traditional style of publishing research data often only shows one side of the coin.
- Most medical illnesses and especially psychiatric disorders are in need of more close investigation of all complex facts.
- With use of a decision-tree one can come to an evaluation of all possible positive and negative outcome of (medical) interventions with calculation of risks and benefits of treatment as well as no-treatment.
- Authors who present only one single outcome of an intervention study should be careful with statements on the usefulness of such an intervention.

Conflicts of interest

All authors declare that they all have no financial or any other kind of personal conflicts with this paper.

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