FOR DEBATE: SHOULD NOVEL ANTIPSYCHOTICS EVER BE USED TO TREAT THE BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)?

Introduction

This issue of International Psychogeriatrics sees the introduction of what I hope will become a regular journal feature: a “for debate” section. Several other journals have a policy of airing two opposing points of view on controversial topics, sometimes followed by a commentary. Although there are some things upon which all (or nearly all!) health professionals working in the field of psychogeriatrics can agree, it is also true that there are a number of issues on which available evidence is too thin, the balance of benefit and cost (or even harm) too delicately poised, or ethical viewpoints too diverse, to allow consensus to emerge. It also seems likely that some of the things that we do as routine or believe as gospel today, may one day turn out to be viewed quite differently (e.g. insulin coma therapy), so I think it is healthy that we should identify such areas of disagreement and rehearse in print the cases for and against certain practices or points of view. The aim is not to make everybody agree, nor solely to entertain our readership with the spectacle of two irreconcilable sides of an argument slogging away at each other until both succumb to a technical knockout (rather like the TV program, Monty Python’s Flying Circus, which proposed a show called A Brick Wall in which two people of utterly opposed views would throw bricks at one another in front of a studio audience!), but rather, by outlining what is known and how it can be viewed, to assist us all in better understanding some of the difficult issues faced by our discipline, and to further comprehension and respect of divergent points of view.

The International Psychogeriatric Association (IPA) has long been at the forefront of attempts to define, assess, research and manage the thorny problems associated with the Behavioral and Psychological Symptoms of Dementia (BPSD) (Finkel et al., 1996). One particular area of concern has been the widespread use of powerful drugs to “treat” these symptoms, despite what has been until the last decade or so, a very sparse base of evidence regarding the efficacy and safety of commonly prescribed medications. Although a number of recent publications have added considerably to knowledge about the effects (both good and bad) of some drug treatments for some presentations of BPSD (e.g. Brodaty et al., 2003), major concerns were raised in 2003 and 2004 by emerging evidence of a possible raised risk of cerebrovascular adverse events in some dementia patients taking risperidone and olanzapine in placebo-controlled trials. While some people thought that all use of these drugs to treat BPSD
should cease forthwith, others held that this was a precipitate overreaction. It thus appeared that this area of controversy would be a suitable opener for the new “for debate” section and we are fortunate, after a communication sent to various experts in the field, that Clive Ballard and Julia Cream have kindly agreed to present the argument against using novel antipsychotics for patients with BPSD, Ajit Shah and Guk Hee Suh have consented to argue in favour of their use for some patients and Ian McKeith has offered to comment on the debate.

I hope that readers of the journal enjoy and appreciate this new feature and that some of them will contact me with ideas for other “for debate” pieces (preferably with the names of experts willing to counter the argument they propose to put forward).

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Drugs used to relieve behavioral symptoms in people with dementia or an unacceptable chemical cosh?

Background

Over 90% of people with dementia develop behavioral problems or psychiatric symptoms at some point during their illness (Ballard et al., 2002). These symptoms are clearly important, but that does not legitimize widespread use of dangerous treatments.

In the current paper, we will review the efficacy of neuroleptic drugs, outline the evidence emphasizing the enormously harmful effects of long-term treatment and, in the discussion, suggest that we prescribe because of fear of therapeutic impotence and not because of the best interests of the patient. There are alternatives available, we need to use them and develop new alternatives as a priority. Otherwise, there is no hope of progress and we will be having the same debate about neuroleptic use in 20 years. This may be comfortable for prescribers, but would be to the serious detriment of people with dementia.

Given the often catastrophic effects of treatment, in the context of dementia, it is difficult to see how neuroleptic treatment can be in the best interests of anyone other than the harassed doctor making the prescription. Probably the most
appropriate advocates for the “best interests” of the patients are their caregivers. The U.K. Alzheimer’s Society receives numerous phone calls to their helpline, with relatives expressing fear and concern over the side-effects caused by neuroleptics. In addition, large surveys of carers undertaken by the Alzheimer’s Society have highlighted the over-use of neuroleptics and other sedative drugs as one of the most important issues to be tackled, and have rated research to reduce the use of neuroleptics as a key priority. Some of the serious concerns expressed by caregivers are highlighted in the quotes below:

My mother was found to be on three times the recommended dose of risperidone, which resulted in her being asleep on her feet, falling and breaking a hip.

Initially my father was put on medication by his GP and hospital consultants. Each time, I questioned his change of state – zombie-like, lethargic, shaky, etc. Eventually I brought him home to live with me, took him off the medication and he was his old self, as much as he could be in the circumstances. I was told my father needed medication because he got up in the night. In other words, instead of giving him a cup of tea and reassuring chat, he was a nuisance, impinging on their needs.

My mother has dementia and recently attended a stroke unit and was given risperidone. The nurses in the stroke unit had no idea that a warning had been issued about these drugs and in fact said that they use them all the time.

The common view, to varying degrees, has been that my father has been difficult and that drug therapy is the solution. My torment and frustration have been immense. To me it has been obvious that what he has needed, is kindness, sympathetic handling and an understanding of his condition. Unfortunately, staff in homes and hospitals seem to find it easier to cope if all their patients are docile and bed- or chair-bound. Training for care workers to treat these patients as individuals, to respond to their individual needs and to listen to their relatives and carers cannot come soon enough.

If prescribing neuroleptics is really the best option for the patients, why does it cause so much concern to so many caregivers?

**Drug therapies for treating BPSD**

Neuroleptics are usually used as the first-line pharmacological treatment for Behavioral and Psychological Symptoms in Dementia (BPSD), Finkel *et al.*, 1996). In total there are 15 published placebo-controlled studies examining the
treatment of BPSD with neuroleptics. Many of these studies are small, although 4 larger studies (3 with risperidone, 1 with olanzapine) have been published over the last 5 years (Schneider et al., 1990; Ballard et al., 1999; Katz et al., 1999; De Deyn et al., 1999; Street et al., 2000; Teri et al., 2000; Brodaty et al., 2003). Two further placebo-controlled trials with quetiapine, published only in abstract, show benefit on some outcome measures, but not on the primary outcome (e.g. Tariot et al., 2004). It is convention to describe a good outcome as a 30% improvement on a standardized behavioral rating scale in these trials. Using this threshold, across all the trials, approximately 60% of people have a significant response to neuroleptics and 40% improve with placebo, a statistically significant but modest effect-size (Schneider et al., 1990; Ballard and O’Brien, 1999). The results are almost impossible to interpret, as the studies group together a range of dissimilar behavioral and psychiatric symptoms, which probably have different underlying etiologies. A recent Cochrane review of haloperidol, for example, indicated that the evidence for efficacy was much stronger for the treatment of aggression than for other symptoms (Lonergan, 2003). There is also a publication bias, as there are at least 3 unpublished studies (1 risperidone, 1 olanzapine, 1 quetiapine) which have not shown significant benefit. There is also very selective presentation of the results to emphasize positive outcomes. In addition, the required threshold of symptoms is very low in some of the studies, hence the study participants may not reflect the patients in whom these treatments are being considered in clinical practice.

To inform treatment decisions, it is important to understand the time-frame of treatment response. The majority of trials focus on a treatment period of between 4 and 12 weeks. They do not provide evidence of a significant improvement with single doses (hence the practice of as-required medication has no underpinning evidence) or over substantially longer treatment periods. The latter is a concern, as many people treated with these agents are prescribed them over a number of years, particularly as several naturalistic follow-up studies have indicated a poorer outcome of behavioral symptoms in people continuing to take neuroleptics, and 3 recent placebo-controlled withdrawal studies indicate that there is no worsening of behavior when neuroleptic drugs are stopped (Cohen-Mansfield et al., 1999; Bridges-Parlet et al., 1997; Ballard et al., 2004).

**Potential harmful effects of neuroleptics**

**General side-effects**

The very modest benefits of neuroleptic treatment have to be considered in the context of the potentially harmful adverse outcomes. Many of the side-effects, such as parkinsonism, drowsiness, tardive dyskinesia and akathasia are well known
from studies of schizophrenia, although are more frequent and severe in people with dementia (Tune et al., 1991). In addition, tardive dyskinesia and related syndromes are effects which have a higher prevalence and occur with shorter durations of treatment in people with dementia, although the risk appears to be significantly lower with atypical antipsychotics (Jeste et al., 1999). Some of the other side-effects may be also be a little less frequent with atypical antipsychotics, although the evidence for this is very anecdotal and the differences in the severity of key side-effects between typical and atypical antipsychotics are probably exaggerated in the minds of clinicians by slick marketing. Illustrating this point, combining the data from all of the published risperidone studies indicates a doubling of significant extrapyramidal symptoms in risperidone-treated patients compared to those receiving placebo.

**Cerebrovascular adverse events and mortality**

Of particular concern, a recent meta-analysis has indicated a significantly increased risk of adverse cerebrovascular outcomes in people treated with the two most commonly prescribed atypical neuroleptics (risperidone and olanzapine). The Committee for the Safety of Medicines (CSM) in the U.K. has decided that risperidone and olanzapine should no longer be prescribed for the treatment of behavioral symptoms in people with dementia because of the increased risk of stroke (CSM, 2004), with similar advice issued by the European Drug Agency. The higher risk of stroke with risperidone treatment was first described as part of a 12-week study placebo-controlled trial of risperidone for the treatment of agitation in people with dementia (Brodaty et al., 2003). A subsequent analysis of this study and 3 other similar trials confirmed the higher risk of stroke, with an odds ratio of 3. Based upon the evidence, the Number Needed to Harm (NNH) for every year of treatment is between 4 and 14. Although there is less information available for olanzapine, as only 2 trials have been completed comparing olanzapine with a placebo in people with dementia, the risk appears to be similar. The same meta-analysis indicated a twofold increase in all cause mortality with risperidone or olanzapine treatment.

**Other serious adverse-event warnings**

The CSM in the U.K. has twice previously issued safety statements regarding the use of neuroleptics in people with dementia. In 2000, a report indicated that some neuroleptics prolonged the Q-T interval (Reilly et al., 2000), particularly in older people, potentially increasing the risk of arrhythmias and sudden death. In response to this, the CSM advised that thioridazine and droperidol should not be used in older people, including those with dementia (CSM, 2000). It should, however, be noted that many of the other neuroleptics studied also prolonged Q-T interval, but to a lesser degree.
Previously, the CSM commissioned a statement in 1994, recommending very cautious use of neuroleptics in dementia patients, particularly those with a diagnosis of dementia with Lewy bodies (DLB). Patients with DLB, who represent 15–20% of patients with late-onset dementia (Rahkonen et al., 2003), are particularly vulnerable to severe neuroleptic-sensitivity reactions, which occur in 30–50% of DLB patients exposed to these agents, even using low doses or newer neuroleptics such as sulpiride, risperidone and clozapine (McKeith et al., 1992; Ballard et al., 1998; Imamura et al., 1999; Sadek and Rockwood, 2003; Ballard, 2004). These reactions are characterized by a sudden onset of sedation, increased confusion, rigidity and immobility, with substantial reductions in survival, often leading to a fatal outcome within a few days or weeks (McKeith et al., 1992). Importantly, because many people with DLB are misdiagnosed as having Alzheimer’s disease (AD) or vascular dementia (McKeith et al., 2000), these reactions are also a serious consideration in people with clinical diagnoses of most common dementias, particularly when they have experienced persistent psychotic symptoms.

Quality of life
Within reviews of neuroleptic treatment for BPSD, blanket statements are often made linking improvement of BPSD symptoms to improved quality of life (QOL). As QOL has not been measured in any of the clinical trials, this is a completely unfounded assumption. There is however considerable potential for a detrimental impact upon QOL. For example, side-effects such as extrapyramidal symptoms, tardive dyskinesia or falls may cause distress, whilst falls may also lead to serious injury which could impact further upon quality of life. Parkinsonism and sedation may reduce an individual’s potential to engage socially or to participate in activities.

As none of the placebo-controlled trials evaluating the efficacy of neuroleptics for the treatment of BPSD have specifically determined the benefits or detriments upon QOL, the evidence-base for determining the impact of neuroleptic treatment on QOL is hence minimal. A cross-sectional nursing-home study, which examined the relationship between behavioral symptoms, QOL and neuroleptics, using observational methodology (Dementia Care Mapping), identified a significant association between impaired QOL and taking neuroleptic drugs, but no association was evident between QOL and any of the behavioral or neuropsychiatric symptoms examined (Ballard et al., 2001). Although this was a cross-sectional study, it does indicate that the apparent detrimental effect of neuroleptics upon QOL is not merely a consequence of concurrent behavioral symptoms, and implies that this class of treatments has a more detrimental impact upon QOL than the symptoms for which they are prescribed. In addition, in further analyses to examine differences in specific activities,
people taking neuroleptics spent less time passively engaged in activities. In addition, ill-being (well-being scores $<0$) was significantly more frequent in people taking neuroleptics (ill-being: taking neuroleptics, 9 (18%), not taking neuroleptics, 3 (5%), odds ratio 4.0 95% confidence intervals 1.03–15.64). This is of enormous potential importance because the neuroleptic agents had a more detrimental impact upon QOL than the symptoms for which they were prescribed.

A subsequent study determined the impact of discontinuing neuroleptic agents in 100 dementia patients residing in care facilities receiving long-term neuroleptics, but without any active severe behavioral disturbances, in a randomized placebo-controlled design (Ballard et al., 2004). Over the 3-month period of evaluation, there was no difference in the severity of BPSD between groups, but there was a 15% improvement in DCM well-being scores in people withdrawn from neuroleptics, compared to a slight worsening in patients continuing with neuroleptic treatment.

Importantly, there is no evidence at all from any studies that treatment with neuroleptics improves QOL for people with dementia. In the few studies where QOL has been studied, the impact of neuroleptic treatment appears to be detrimental.

Falls

People with dementia are 4–5 times more likely to experience falls than older people without significant cognitive impairment (van Doorn et al., 2003). The consequences are often serious and include fractures (in particular hip fractures), hospitalizations, institutionalization and death (Rowe and Fehrenbach, 2004a). There are also major service utilization and health economic consequences resulting from attendances at Accident and Emergency, hospitalization, surgery and long-term care needs (Scuffham et al., 2003). The majority of people with dementia experiencing a hip fracture never achieve their previous level of functional capacity (Rowe and Fehrenbach, 2004). Most psychotropic drugs substantially increase the risk of falling, with neuroleptics identified as the most important attributable cause of drug-related falls in a recent nursing-home study (Kallin et al., 2004). It is a major flaw in all of the placebo-controlled trials of neuroleptic agents that falls have not been systematically evaluated and will therefore have been seriously underestimated (Ballard et al., 1999). The impact of neuroleptics upon falls is therefore a much more serious consideration than has been highlighted in the clinical trial literature.

Accelerated cognitive decline

Also of major concern in the context of dementia, an influential study reported a doubling in the rate of cognitive decline for patients taking neuroleptics, with
a mean annual decline on the Mini-mental State Examination (MMSE) of 11 points per annum in people taking these agents (McShane et al., 1997). Subsequently, it has however been demonstrated that even using an insensitive instrument such as the MMSE (Folstein et al., 1975), haloperidol was associated with significantly greater cognitive decline across the course of a 6-week randomized placebo-controlled trial (De Deyn et al., 1999). Very recently, a six-month placebo-controlled trial of an atypical neuroleptic for people with agitation in the context of dementia has indicated that patients treated with an atypical neuroleptic had a significantly worse cognitive outcome over six weeks and six months, than those receiving placebo (Ballard et al., 2005). The accumulating evidence from randomized controlled trials therefore supports the study of McShane et al. (1997), in suggesting that neuroleptics, including atypical agents, have a very detrimental impact upon cognition. Given the effect-size, which is substantially larger in the opposite direction than the magnitude of improvement with any of the currently licenced anti-dementia drugs, we believe that long-term treatment with neuroleptics should only be considered in extreme circumstances and with the informed consent of the next of kin.

Evidence is accumulating to indicate that the detrimental impact upon cognition is underpinned by key neurochemical and neuropathological changes that are exacerbated by neuroleptics. Studies in Newcastle indicate a greater loss of striatal dopamine and nicotinic acetylcholine receptors, which are associated with nigro-striatal dopaminergic neurones, in dementia patients treated with neuroleptics (Piggott et al., 1998; Court et al., 2000), whilst a small prospective study in Oxford indicated a reduction of 5-hydroxytryptamine (5HT) in the frontal cortex of AD patients taking typical neuroleptics (8 patients on 3 different neuroleptics for 8 months prior to death) (Chen et al., 1996). Furthermore, a recent study has suggested that patients taking neuroleptics have a substantially greater burden of neurofibrillary tangles at post-mortem in key brain areas such as the temporal cortex, even in regression analysis controlling for duration of dementia and neuropsychiatric symptoms (Ballard et al., 2004).

It will be important to determine the potential mechanisms of this detrimental effect, as some neuroleptics may have a more pronounced impact than others, depending upon specific characteristics such as the potency of D2 antagonism or anti-muscarinic properties, with implications for prescribing practice. Recent work in animal models has suggested that neuroleptics reduce the expression of Brain Derived Neurotrophic Factor (Chlan-Fourney et al., 2002), probably mediated by D2 receptor antagonism, which may result in increased senile plaque and neurofibrillary tangle formation (Coffey et al., 1997). In addition, a clinico-pathological study in Parkinson’s disease has indicated that anti-muscarinic agents increase the accumulation of tangles (Perry et al., 2003).
Summary

As clinicians we talk about “the best interests of our patients”. How can a treatment which doubles the rate of cognitive decline, triples the rate of stroke, doubles mortality, substantially increases falls and fractures and reduces quality of life be beneficial, especially, as in real life, once neuroleptics are started they are rarely discontinued with cumulative adverse effects?

As there is clearly no rational reason for prescribing, we need to consider other explanations. We would suggest the following:

Therapeutic impotence:

Doctors, especially specialists feel they need to do something, and prescribing a familiar drug is the easiest option.

Ignorance:

Doctors are either unaware of the substantial evidence of harm with neuroleptics or are swayed by slick marketing information, portraying atypical neuroleptics in an “over-safe” light that does not reflect the actual data.

Placebo effect:

If neuroleptics are prescribed, the majority of patients experience an improvement in BPSD symptoms. This reinforces the apparent value of this practice, as we like to take the credit for any improvements that occur. The reality is that the majority of people would have experienced a comparable improvement with monitoring.

Bowing to pressure:

Sometimes the pressure to respond can be great, and a prescription is an easy way to relieve the pressure. This is understandable, and reflects a similar phenomenon to that of general practitioners prescribing antibiotics for sore throats. In neither situation does it represent good practice.

Lack of skills to implement non-pharmacological alternatives:

The main evidence for alternative treatment options are for therapies that by and large are not a core part of the physician or psychiatrist’s skill-base, such as psychological interventions (Cohen-Mansfield and Werner, 1997). Doctors therefore feel uncomfortable pursuing these options. Why for example is so little time spent on the non-pharmacological interventions that everyone agrees should be the first line of treatment for BPSD in people with dementia? It is largely assumed that the “enlightened clinician has already appropriately assessed and diagnosed the patient and exhausted all the possible environmental and behavioral interventions before resorting to the prescription pad.” Accumulating evidence clearly indicates that the
need for psychotropic medication is substantially reduced by proactive services or interventions which can provide training and promote psychological, social and environmental and sensory interventions (e.g. Rovner et al., 1996; Ballard et al., 2002; Burns et al., 2002). The prescription but is an easy but not an acceptable alternative.

Over-adherence to prescribing guidance:

There are pharmacological alternatives to neuroleptics if a prescription is needed. Although the evidence for the more promising alternatives needs to be developed much further, drugs such as cholinesterase inhibitors may offer a much less harmful alternative. The reluctance of clinicians to use cholinesterase inhibitors in this way is puzzling, and presumably is because of the culture of “guidance-prescribing” that has evolved around these agents.

If the treatment of BPSD is to move forward, we need to challenge the way we have always done things, examine the evidence and move forward with new and flexible multi-disciplinary approaches if we are truly to look after the “best interests of our patients”.

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A case for judicious use of risperidone and olanzapine in behavioral and psychological symptoms of dementia (BPSD)

Introduction

Behavioral and psychological signs and symptoms of dementia (BPSD) include disorders of behavior, mood, thought content and perception (Burns et al., 1990a, b, c, d; Foli and Shah, 2000). BPSD are common (Foli and Shah, 2000) and can cause distress to patients, informal carers and professionals, and lead to institutionalization and over-medication (Shah, 1999). Both non-pharmacological and pharmacological treatment strategies have been utilized to improve
BPSD. Despite the recent controversy surrounding the use of olanzapine and risperidone for BPSD, a case for judicious use of these drugs is rehearsed below.

**Recent controversy surrounding use of risperidone and olanzapine in the treatment of BPSD**

In March 2004, the U.K. Committee of Safety of Medicines (CSM) informed clinicians that risperidone and olanzapine should not be used to treat BPSD because of increased risk of strokes with both drugs and increased risk of mortality with olanzapine (CSM, 2004). The following evidence was cited: (i) a meta-analysis of randomized placebo-controlled studies of risperidone in dementia demonstrated a threefold increase in strokes; and, (ii) a pooled-analysis of randomized placebo-controlled studies of olanzapine in dementia demonstrated a threefold increase in strokes and a twofold increase in mortality. The CSM did not provide details of the meta-analysis for risperidone or the pooled-analysis for olanzapine and listed no references. Moreover, they concluded that “the magnitude of this risk is sufficient to outweigh likely benefits in the treatment of behavioral disturbances associated with dementia, and is a cause for concern in any patient with a high baseline risk of stroke”.

The CSM provided the following prescribing advice:

- Both drugs should not be used to treat behavioral symptoms of dementia (essentially referring to “disorders of behavior” in the BPSD classification).
- Use of risperidone for the management of acute psychotic conditions in dementia should be limited to short-term use under specialist advice.
- Prescribers should consider carefully the risk of cerebrovascular events before treating any patient with a previous history of stroke or transient ischaemic attack (TIA). Furthermore, consideration should be given to other risk factors for cerebrovascular disease including hypertension, diabetes, atrial fibrillation and current smoking.

Similar concerns about risperidone were previously raised in Canada and the U.S.A. (Smith and Beier, 2004). However, concerns about olanzapine are new. Clinicians in the U.K. and elsewhere were alarmed, as these two drugs were widely used to treat BPSD because of evidence of efficacy and generally accepted better side-effect profiles than conventional neuroleptics, which show more severe and frequent adverse events like parkinsonism, tremor, dystonia, sedation, postural hypotension and anticholinergic effects (Saxe, 2004).
What is the evidence?

Concerns in the U.S.A. were based on data from four placebo-controlled studies involving 1230 patients with dementia (Smith and Beier, 2004). Pooled data showed that the incidence of both “serious” and “non-serious” cerebrovascular adverse events (CVAEs) was higher in the risperidone than the placebo group. A letter to Canadian doctors raised concerns that the rate of CVAEs was 4% in the risperidone group, compared to 2% in the placebo group, and the post-marketing database of 2.4 million patient years indicated 37 cases of CVAEs with 16 fatalities (Smith and Beier, 2004).

Janssen-Cilag, in response to our personal enquiry, stated that a pooled-analysis of six placebo-controlled trials involving elderly patients with dementia indicated a threefold increase in CVAEs in the risperidone group (3.3%) compared to the placebo group (1.2%), with an odds ratio of 2.96 (95% confidence interval 1.33–7.45) (Personal Communication from Janssen Cilag, 2004). The incidence of strokes and TIAs in the risperidone and placebo groups were 1.6% and 0.6% respectively. Three of these studies have been published in peer-reviewed journals (Katz et al.,1999; De Deyn et al., 1999; Brodaty et al., 2003). However, the other three studies appear not to have been published and, therefore, have not been subject to peer review. Four of the studies, including the three published studies, were for the treatment of all BPSD and two of the three unpublished studies were of psychosis in dementia. All three published studies included subjects with Alzheimer’s disease (AD), vascular dementia and mixed dementias in varying combinations; the precise diagnostic composition of the unpublished studies is unclear. Dosage and duration of treatment with risperidone were not associated with risk of developing CVAEs. Also, there was no clear evidence of a temporal relationship between the prescription of risperidone and CVAEs (Finkel et al., 2004; Greenspan et al., 2004; Herrmann, 2004).

Lilly, in response to our personal enquiry, stated that in a pooled-analysis of five placebo-controlled trials of olanzapine for dementia-related psychosis, involving 1184 subjects on a mean dose of 4.4 mgs of olanzapine (328 patient years of exposure), 1.3% of the olanzapine group and 0.4% of the placebo group had CVAEs (Personal Communication from Lilly, 2004). After adjusting for age, sex and dementia type, patients in the olanzapine group were reported to have a higher incidence of CVAEs. Subjects with CVAEs in both the olanzapine and placebo groups had pre-existing risk factors for CVAEs, and age over 75 years and vascular or mixed dementias were additional risk factors. Also, the incidence of mortality was increased in the olanzapine group (3.5% versus 1.5%). Mortality was increased, independent of the risk factors for mortality as described in the literature (including age over 65 years, dysphagia, sedation, malnutrition and
dehydration, pulmonary conditions and concomitant use of benzodiazepines). Dosage of olanzapine and duration of treatment were not predictors of mortality. The precise dementia types included in these studies are unclear. It is unclear which studies were included in the pooled-analysis and whether they were subject to peer review. It is probable that a 6-week (Street et al., 2000; Clark et al., 2001) and a 10-week (De Deyn et al., 2004) randomized, placebo-controlled study of olanzapine in the treatment of BPSD in nursing-home subjects with AD were included.

**Flaws in the evidence**

Neither the CSM nor the personal correspondence from Janssen-Cilag and Lilly provided detailed methodology for the meta-analysis and the pooled-analysis. In the Australasian study, there were five subjects with strokes and one with TIA in the risperidone group (Brodaty et al., 2003). Five of these subjects had either vascular dementia or mixed vascular dementia and AD, and all subjects had predisposing risk factors for CVAEs (5 had prior strokes, 5 had hypertension and 1 had atrial fibrillation). Similarly, Lilly's pooled-analysis for olanzapine revealed that all subjects in the olanzapine or the placebo group who developed CVAEs had pre-existing risk factors for CVAEs. It may be that risperidone or olanzapine alone are not responsible for the CVAEs, but a history of previous CVAEs and associated risk factors may, in combination with these drugs, lead to CVAEs. Methodologically, the effects of risk factors for CVAEs can be allowed for by either excluding subjects with vascular dementia or mixed dementia and risk factors for CVAEs or by stratifying at the randomization stage for these variables (Brodaty et al., 2003). Many factors (including age, sex, dementia type, severity of dementia, severity of cognitive impairment, severity and type of BPSD, previous history of CVAEs, and previous history of cerebrovascular risk factors like diabetes, smoking, cardiac disease and hypertension) can influence the outcome of meta-analysis or pooled-analysis, unless they are adequately controlled for (Suh and Shah, 2005), because, inadvertently, more or fewer subjects with cardiovascular risk factors could have been randomized into the active treatment group. Lilly appears to have attempted to control for some of these variables in their pooled-analysis for CVAEs and mortality, although the precise methodology was not described. There is no evidence from Janssen-Cilag's analysis that these influential variables were adequately controlled for. Moreover, one clinical study reported that adverse events in general were associated with cardiovascular disease and its treatment (Zarate et al., 1997). The importance of controlling for influential variables is further illustrated by our recent one-year prospective, longitudinal and naturalistic study of Korean nursing-home residents with AD, vascular dementia and mixed dementia (Suh
and Shah, 2005). After controlling for influential variables (like age, gender, severity of dementia, medical morbidity, duration of dementia, MMSE scores, BEHAVE-AD scores for BPSD), using appropriate statistical techniques, the mortality rate in subjects with AD was lower in the group who received neuroleptics (almost all subjects received risperidone at least) than in the group not receiving neuroleptics (Suh and Shah, 2005). In the same study for vascular dementia, there was no evidence of an increased risk of mortality in the neuroleptic group when other influential variables were controlled for. All the published double-blind randomized studies of these two drugs have largely been of nursing-home populations who are likely to have higher prevalence of medical morbidity, risk factors for CVAEs and mortality, independent of neuroleptics anyway.

The precise definition of CVAEs and the standardized ascertainment of the diagnosis of CVAEs is unclear in the published studies of both risperidone and olanzapine. Were CVAEs operationally defined? Were CVAEs diagnosed using standardized instruments and diagnostic criteria? Were the diagnoses of CVAEs supported by evidence from neuroimaging and clinical examination by a neurologist or a geriatrician? Was there any further evidence from post-mortem examination of subjects who died? The answer to all these questions for the published studies is “no,” and these questions for the unpublished studies cannot be answered. Most studies appear to rely on self-reports of adverse events, which may be biased towards misidentifying CVAEs instead of other adverse events like falls. Four randomized, double-blind studies simply stated that adverse events were documented throughout the study without any data on the method of ascertaining adverse events (Brodaty et al., 2003; De Deyn et al., 1999; Katz et al., 1999; 2004; Street et al., 2000), although they were classified according to WHO-preferred terms in one study (Brodaty et al., 2003). Furthermore, none of the published studies was designed to monitor adequately for CVAEs. A further methodological issue was reported in a double-blind study of risperidone and placebo for the treatment of BPSD, whereby treatment discontinuation and completion rates were similar in subjects receiving placebo and risperidone up to 1mg per day (Katz et al., 1999); the authors concluded “that it may, at times, be difficult to distinguish between adverse events of risperidone and spontaneously occurring adverse events”.

Pooled-analysis of data from different studies of differing designs, medication dosages, study durations, number of study arms (risperidone or olanzapine, placebo and another neuroleptic like haloperidol), proportion of subjects with AD, vascular dementia and mixed dementia, study-settings (e.g. institution), previous CVAEs, presence of risk factors for CVAEs, and methods of measuring adverse events like CVAEs are difficult to interpret (De Deyn and Katz, 2000), particularly when important influential variables are not controlled for in the
data analysis. Moreover, pooled-analyses simply demonstrate an association and do not necessarily imply causation (Smith and Beier, 2004). The dosage and duration of treatment with olanzapine and risperidone did not influence CVAEs and mortality rates, and there is no evidence of a clear temporal relationship between prescription of these two drugs and development of CVAEs or death. In one randomized double-blind study comparing intramuscular olanzapine, lorazepam and placebo in acutely agitated subjects with AD and vascular dementia, there were no differences in side-effects between the three groups (Meehan et al., 2002): intramuscular administration of drugs is more likely to illustrate any immediate temporal relationship between prescription of the drugs and adverse-events. Furthermore, studies used in the pooled-analysis and meta-analysis were not specifically designed to either examine the null hypothesis that risperidone or olanzapine do not increase the risk of CVAEs or mortality, or the unidirectional hypothesis that they do so (Smith and Beier, 2004). Also, some of the studies used in the pooled-analysis and meta-analysis have not been formally published and therefore have not been subject to peer-review. Similarly, findings of the pooled-analysis and meta-analysis have also not been subject to peer-review with formal publication. In addition, in the pooled-analysis of risperidone, there was an insufficient number of adverse events to examine vascular dementia and AD separately and therefore all dementias were amalgamated; this is an important methodological issue as different adverse events may occur in different dementia types.

Most study samples were heterogeneous, with differing diagnostic combinations of AD, vascular dementia and mixed dementias. As illustrated earlier in the Australasian study, cases with CVAEs were those with vascular dementia and risk factors for CVAEs (Brodaty et al., 2003). Furthermore, data from the pooled-analysis were used to provide a blanket ban on all dementias when other types (e.g. alcohol-related dementias) have not been examined. However, it is conceded that evidence of efficacy for these drugs in other types of dementia is limited.

Other problems with withdrawal of these drugs for BPSD

If these two drugs are banned for treating BPSD then there is the possibility that clinicians will either use “old-fashioned” neuroleptics (from the phenothiazine, butyrophenone or thioxanthene groups, or sulpiride), or other novel neuroleptics (like quetiapine, amisulpride, aripiprazole and clozapine). Older neuroleptics have been shown to have modest efficacy in BPSD in a meta-analysis (Schneider et al., 1990), but their contribution to CVAEs and mortality has not been critically examined. In general, the efficacy and side-effect profile of older neuroleptics in the treatment of BPSD has been poorly studied.
Placebo-controlled randomized studies with older neuroleptics were largely conducted well over a decade ago and often were methodologically flawed (for example standardized instruments to measure BPSD were not used). Also, older neuroleptics are well recognized to have undesirable side-effect profiles, including sedation, orthostatic hypotension, anticholinergic side-effects and extrapyramidal side-effects; the detailed account of side-effects of neuroleptics by Ballard and Cream (see above) strongly applies to older neuroleptics. The efficacy and safety of the novel neuroleptics (other than risperidone and olanzapine) has not been examined in placebo-controlled, randomized double-blind studies for BPSD. It is, therefore, possible that findings similar to those for risperidone and olanzapine may apply to both older neuroleptics and other newer neuroleptics, and there may be other unrecognized problems simply due to paucity of studies. Moreover, haloperidol was reported to have a higher risk of CVAEs compared to placebo (Personal communication from Janssen-Cilag, 2004). By discouraging the use of olanzapine and risperidone, other drugs which are less well researched may be blindly used and lead to similar and other, hitherto, unidentified adverse events. Also, in the risk-benefit evaluation before prescribing, consideration should be given to other problematic side-effects of older neuroleptics (Finkel, 2004).

All the studies included in the meta-analysis and pooled-analysis originate from developed countries. These findings may not be applicable to developing countries, where the epidemiology and risk-factor profile for AD, vascular dementia and cerebrovascular disease may be different from western populations (Suh and Shah, 2001). This is supported by our recent randomized double-blind crossover study of risperidone and haloperidol in the treatment of BPSD in Alzheimer’s disease, vascular dementia and mixed dementia in Korean subjects (Suh et al., 2004). This study observed no increase in CVAEs in the risperidone group (Suh et al., 2004). These findings, however, could be interpreted to be due to a similar risk for CVAEs in the haloperidol group.

There is little justification for suggesting that these drugs should not be used in subjects with CVAs and TIAs in patients without dementia, given that the evidence emerges from studies of BPSD in dementia. Although, it is not unreasonable to consider cardiovascular risk factors in the equation to prescribe, there is no evidence that the risk of CVAEs or mortality is increased in psychiatric disorders other than dementia (Personal Communication from Janssen Cilag, 2004). Furthermore, there is no clear evidence from extensive use of these drugs in younger-aged patients in functional disorders like schizophrenia and mania, of increased risk of CVAEs or mortality (Personal Communication from Janssen Cilag, 2004).

The suggestion, from the U.K. CSM, that risperidone could be used in the short-term for psychosis in dementia is flawed and paradoxical. Surely if
risperidone unequivocally increases the risk of CVAEs, then it should not be used at all. On the other hand, if risperidone can be used in the short-term for psychosis in dementia, then it is unclear why it cannot be used in the longer-term for psychosis in dementia and for other types of BPSD, particularly as there is no relationship between dosage and duration of exposure and CVAEs.

**Ethical considerations**

What should be done about continuing the prescriptions of these two drugs in patients already receiving them with clinical evidence of effectiveness? CSM advice, supported by subsequent guidelines issued jointly by the Royal College of Psychiatrists, British Geriatrics Society, and The Royal College of General Practitioners, suggested that those patients should be reviewed, and judgement on the subsequent continuation of these two drugs should be based on the clinical circumstances of each case, and be discussed with the patient and their carers. Surely, if the views of patients and carers are considered in reviewing the need to continue prescribing these two drugs, then new patients with BPSD requiring pharmacotherapy should also be offered such a choice to make an informed decision on new use of these drugs (Wooltorton, 2002), rather than a blanket ban. After all, patients and carers should be able participate and help make an informed decision on their care. Patients and their carers should be offered a choice to receive treatment from drugs which have well-established efficacy. They should also be given a choice between possible increase in the risk of CVAEs and mortality with risperidone and olanzapine, and unidentified similar risks and other risks with other drugs, as well as their unestablished efficacy. This is important because caregivers in the community spend more time managing behavior disturbance than any other activity (Max et al., 1995).

**The future**

There are many clinical studies (Madhusoodanan et al., 1995; 2000; Berman et al., 1996; Goldberg and Goldberg, 1997; Zarate et al., 1997; Frenchman, 2000; Negron and Reichman, 2000; Verma et al., 2001; Martin et al., 2003; Wancata, 2004a; 2004b), open-label studies (Davidson et al., 2000; Edell and Tunis, 2001) and randomized studies (Katz et al., 1999; De Deyn et al., 1999; 2004; Street et al., 2000; Chan et al., 2001; Clark et al., 2001; Brodaty et al., 2003; Suh et al., 2004) of risperidone and olanzapine in a range of disorders, including different dementias, bipolar affective disorder, schizophrenia and schizoaffective disorders in the elderly. Data from all these studies need to be examined simultaneously to draw a result, after controlling for the afore-mentioned influential variables for adverse events, including CVAEs and mortality. Such
“pooled-analysis” of adverse events from a range of study types may provide more robust and convincing evidence. Large naturalistic studies of representative clinical populations can also provide valuable data. This is illustrated in a study of 938 subjects treated with risperidone for BPSD by their general practitioners in Austria (Wancata, 2004a, 2004b); there was only one case (0.1%) of stroke with death.

There is clear evidence of efficacy in the treatment for BPSD for risperidone and olanzapine (although the evidence for risperidone is better). However, as reasoned by Ballard and Cream (above), there is no doubt that non-pharmacological interventions need to be considered first in the management of BPSD (Wooltorton, 2002). These interventions include treatment of intercurrent medical illness, correction of sensory deficits, evaluation of drug interactions and side-effects of prescribed drugs, identification and treatment of delirium, control of pain, support for carers, interventions directed at carers, psychological approaches in treating BPSD, aromatherapy, light therapy (although not widely available), reality-orientation therapy, validation therapy, reminiscence therapy, music therapy, day care, nursing the dementia-patient in an appropriate environment with appropriately skilled staff (e.g. nursing home), respite care and carer training. There is evidence that some non-pharmacological interventions are efficacious and others are not (Doody et al., 2001; Camp et al., 2002). However, in contrast to Ballard and Cream’s view, despite non-pharmacological interventions, there may be occasions when pharmacological interventions are needed in the treatment of BPSD. Moreover, pharmacological interventions can complement non-pharmacological interventions, and the two are not mutually exclusive. Furthermore, if the burden of disease is small and there are adequate alternative treatment options, recommendations to eliminate certain treatments from the physician’s toolbox may seem reasonable. However, if the burden of disease is high (as is case for BPSD) and treatment difficult, any outright ban of specific treatments (like pharmacological treatment for BPSD) may not be the most prudent approach. Clearly, for disorders of mood, antidepressants and/or mood stabilizers may be appropriate. However, for disorders of behavior, perception and thought content neuroleptics may be needed.

The arguments against a complete ban on these drugs as rehearsed above can be summarized as follows: (i) the risk of CVAEs and mortality have been derived from unsophisticated statistical analysis, without adequately controlling for influential variables discussed earlier; (ii) increased risk of CVAEs appears to be confined to subjects with vascular dementia or mixed dementia and those with cerebrovascular risk factors; (iii) many of the studies used in the meta-analysis and pooled-analysis appear not have been published in peer-reviewed journals and these analyses also have not been published after peer-review; (iv) CVAEs have not been formally defined, and reliable and valid methods of ascertaining
CVAEs have not been used; (v) the cited studies of these two drugs were not designed and powered to examine the relationship between prescription of these two drugs and the risk of CVAEs and mortality; (vi) there is no clear relationship between risk of CVAEs and mortality and the duration of exposure and dosage of these two drugs; (vii) there is no clear evidence of a temporal relationship between prescription of these two drugs and development of CVAEs and death; and, (viii) patients with a pure dementia type have not been examined, except in two studies. There is a serious risk that if clinicians are discouraged from using these two drugs in the treatment of BPSD, they will either use older neuroleptics (with modest efficacy, less desirable side-effect profiles and poorly studied risk of CVAEs and mortality, which may be worse or comparable at best), or other newer neuroleptics (without evidence of efficacy and possibly similar problems, which to date have not been studied), and patients could be exposed to unidentified side-effects with these drugs.

There is a case from the evidence that these two drugs should not be used to treat BPSD in patients with vascular dementia and those with previous CVAEs and cerebrovascular risk factors. However, in patients with AD and without previous CVAEs and cerebrovascular risk factors, the evidence is debatable. After exhausting non-pharmacological treatment strategies for BPSD in AD, if a decision is made to consider neuroleptics, patients and carers should be given a choice. Patients and carers should be made aware of the following issues: (i) the evidence provided by CSM and the manufacturers of these two drugs and the flaws in the evidence discussed earlier; (ii) the possibility that similar side-effects may occur with older neuroleptics and other newer neuroleptics, and the evidence for this is absent, due to the paucity of studies; and, (iii) absence of evidence of efficacy with other neuroleptics and, at best, modest efficacy for older neuroleptics with an undesirable side-effect profile. Otherwise there is a risk of denying patients efficacious treatment without robust evidence of increased risk of CVAEs and mortality. It goes without saying that if these two drugs are prescribed, then treatment should commence with low doses, and any increment should be in low doses and slow, and careful monitoring of side-effects should be in place. Ideally, treatment should be initiated and monitored in secondary care. Until further research emerges, clinicians should weigh up carefully the risk and benefits of discontinuation or commencement of treatment with these drugs (Smith and Beier, 2004). Data on duration of treatment with these two drugs are not available (most trials of 4 to 12 weeks) and, therefore, efforts should be made to discontinue treatment at the earliest opportunity. Ballard and Cream raise the possibility of prescribing cholinesterase inhibitors for the treatment of BPSD; the background to this is the evidence that cholinesterase inhibitors have efficacy in the treatment of BPSD in Lewy body dementia, although the evidence for other dementias is less robust. However, many of the
arguments they rehearse against the use of neuroleptics, including side-effects and unequivocal evidence of efficacy, may also apply to cholinesterase inhibitors. Ballard and Cream provide several explanations for clinicians prescribing neuroleptics in dementia at the expense of non-pharmacological interventions. These include therapeutic impotence, ignorance, placebo effect and bowing to pressure. Lack of training and knowledge in the use of non-pharmacological interventions is not a reason to avoid pharmacological treatment. This can be improved with adequate training in the treatment of BPSD with both pharmacological and non-pharmacological methods at undergraduate and postgraduate levels for doctors and other professionals in psychogeriatrics, geriatrics, general practice and other specialities working with the elderly. There is an urgent need to publish all data on these two drugs through the usual peer-review process and a sophisticated analysis using appropriate statistical methodology of an amalgamation of clinical studies, open-label studies and double-blind randomized studies.

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Commentary

Ballard and Cream, henceforth referred to as the “noes”, and Shah and Suh (the “ayes”), express differing views on the matter of prescribing atypical antipsychotics to patients with dementia. They provide new and useful information which demonstrates that the psychogeriatric community is striving conscientiously to improve the management of BPSD. Despite some strong words, the “noes” ultimately admit that “long-term treatment with neuroleptics should (only) be considered in extreme circumstances and with the informed consent of next of kin”. Although this conflicts with their assertion that “there is clearly no rational reason for prescribing . . . (neuroleptics),” it suggests that the debate is really about defining where the threshold for prescribing neuroleptics to people with dementia should lie, rather than whether we should or shouldn’t use the drugs at all. The “ayes” proffer the liberal opinion that clinicians should offer details about efficacy and side-effects to patients and carers in order that
they might “weigh up carefully the risks and benefits” of treatment. It is not said in what proportion of cases with BPSD this avenue should be taken, nor is it clear how the final decision will be reached. This is too simplistic a solution. We cannot deal with this issue just by passing the buck to the patient and carer.

How much do we really know about the efficacy and side-effects of atypicals in BPSD? The “ayes” quote new information from the pharmaceutical companies concerned, and use it to demonstrate just how difficult to interpret are the findings about stroke, TIA and other cerebrovascular adverse events (CVAE) following olanzapine and risperidone use. It is the usual Catch-22 of evidence-based medicine – most evidence is flawed in some way and therefore, it is argued, cannot be relied upon. Gazing ever further in to the evidence simply increases our sense of uncertainty. One reads for example that the rate of CVAE is three times higher in placebo-treated patients in the risperidone dataset (1.2%), compared with olanzapine (0.4%). We recognize the sampling and assessment differences that probably led to these differences, but how do we extrapolate from these figures when we speak to our patients and carers about “real” levels of risk? If one closes one’s eyes for a moment (sorry “ayes”!) to the inevitable methodological shortcomings of the various trials, it does seem that the company-sponsored trials consistently show a 2–3× higher rate of CVAEs on active drug. Pre-existing risk factors for CVAE seem (unsurprisingly) to be associated with a higher incidence of actual CVAEs following treatment with atypicals, but this association holds also in placebo-treated patients. Advice to be particularly cautious in patients with CVAE risk factors is therefore prudent, but, since it will apply to the majority of patients, may be of little help in guiding practice.

There are of course many side-effects of neuroleptics apart from CVAEs, and the “noes” summarize these very well. Falls, parkinsonism, accelerated cognitive decline and “ill-being” should correctly be added to the list of possible adverse outcomes of treatment. Others not mentioned include weight gain and disruption of blood glucose control. Similar effects occur in people with schizophrenia and bipolar disorder. We do not know whether the incidence of CVAEs is increased by atypical antipsychotics in older patients with these other diagnoses, but we are advised to continue to prescribe atypical antipsychotics to them. This raises the suspicion that over-prescriptive guidance about treating people with dementia and BPSD is being influenced by factors other than the purely evidence-based or scientific.

Both sides describe the effects of atypicals in BPSD as “modest” (ayes) or “very modest” (noes), but this apparent convergence of opinion conceals the fact that the assessment of efficacy is where the greatest uncertainty lies. When does a benefit in BPSD become a useful one, and how does one measure it? One can argue the scientific case for assessing the impact upon specific symptoms
e.g. the Cochrane review, which concluded that the evidence for efficacy of haloperidol was much stronger for aggression than for other items. An equally compelling case can be made however for judging the outcome of treatment interventions by a global assessment of the person’s whole behavior and well-being e.g. in the Dementia Care Mapping studies in nursing homes. Whichever method is adopted, the results are inevitably presented as group-effects and invariably displayed as means and confidence intervals. These statistics, designed as they are to demonstrate differences between drug and placebo, primarily for regulatory or marketing purposes, tell us only a limited amount about the response of individual people to different treatments. Such information cannot be usefully applied to the management of an individual patient, as occurs in clinical practice. Responder analysis is a more appropriate way in which to present treatment data of this type. But responder analysis of large trials is usually limited to reporting the proportion of people experiencing some benefit from treatment, compared with the proportion staying the same or worsening, i.e. the analysis remains focused around a mid-point. This mid-point, which essentially represents little or no change with treatment, is unfortunately a poor place to look when trying to decide about risks and benefits. Our focus should instead be upon those patients who either improve a lot following treatment or on those who deteriorate markedly. Risk-benefit analysis then becomes much more straightforward. Giving an atypical antipsychotic to a person with BPSD probably can be justified if the stated intention is to continue the treatment only if there is substantial improvement which is considered sufficient to justify the potential risks. Such an approach would not need to be restricted only to “extreme cases” as the “noes” would have it, although might be considered only when other, lower-risk interventions had failed and behavioral disturbance was felt to be severe enough to demand treatment.

I suspect that many practicing clinicians would share such a view and justify it in the name of clinical pragmatism or something similar. Of course we must be careful with our treatments. Of course we don’t want to do harm to people and it probably does us no harm to be reminded of our responsibilities now and again. But we live in such a risk-averse culture that many things which pose even a slight possibility of causing harm are unnecessarily dealt with by legislative prohibition. As professionals, we should be able to manage risk, rather than simply to step away from it. The “noes” write emotively of our therapeutic impotence, our ignorance, our susceptibility to persuasion by slick marketing and our tendency to bow to pressure. It is you and me to whom they are referring. It is us they accuse of using the “chemical cosh”. Language like this is deliberately provocative, and is unhelpful. It may well express the rightful anger of people who have experienced the injudicious use of antipsychotic drugs, but has no place in a professional debate. It can serve only to increase the adoption of polarized
views, making it harder to persuade “less enlightened clinicians” to change their practice. Similar anecdotes to those presented about drug-prescribing can be told about all aspects of dementia care, not least the negative attitudes, insensitive approaches and ill-considered responses to which people with dementia are so often exposed. Putting severe restrictions upon the use of antipsychotics for people with dementia will create a ghetto, not only for those deemed so severely disturbed as to require them, but also for the prescribers and associated carers, who are seen to be condoning this “extreme” practice.

We already know that we should prescribe with caution, and the collection and analysis of large amounts of additional “evidence” is, in my view, unlikely to tell us much more about which patients with BPSD will benefit substantially from treatment (a minority), which will experience severe side-effects (a minority) and which will experience little in either direction (the majority). The definitive guidance from the U.K. CSM that risperidone or olanzapine should not be used for the treatment of behavioral symptoms of dementia has placed all parties in a difficult position. I would not encourage you to contravene the guidance and thereby expose yourself to the possibility of litigation. But I would encourage you to challenge it through your professional bodies and organizations in order to achieve a more balanced approach.

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