CASE AUTH/2723/7/14

CLINICIAN v NAPP

Promotion of BuTrans

A consultant psychiatrist with an NHS trust, complained about a BuTrans (buprenorphine transdermal patch) advertisement and website created by Napp Pharmaceuticals which raised awareness of the difficulty of treating pain in patients with dementia. The complainant also provided a copy of a detail aid.

BuTrans was indicated for the treatment of non-malignant pain of moderate intensity when an opioid was necessary for obtaining adequate analgesia. BuTrans was not suitable for the treatment of acute pain.

The complainant submitted that agitation and aggression were particularly burdensome for carers. Agitation had multiple causes, one of which was pain. Better pain relief was likely to reduce agitation in dementia and a pain relieving patch made sense because compliance was easier.

The complainant quoted text from the www.butrans.co.uk website which he/she alleged implied that there was evidence to support the use of BuTrans in dementia which was misleading.

The complainant stated that the published evidence about the use of BuTrans in dementia derived from a single trial, various aspects of which had been published (Husebo *et al* 2011, Husebo *et al* 2014, and Sandvik *et al* 2014). In summary, patients were recruited on the basis that they were agitated, not because they had pain; only 57% were recorded as having clinically relevant pain. BuTrans was used as part of a stepped pain relief protocol in which patients first tried paracetamol, then opiate, then BuTrans, then pregabalin. The majority only took paracetamol. Of those allocated to the treatment arm (n=103), only 29 (28%) received a BuTrans patch. Some patients went straight onto the patch because of trouble swallowing but the three papers differed in their accounts of whether this applied to all of those who started the patch.

The complainant stated that mean scores for pain were not significantly different between control and BuTrans at week 2 or week 4 but were significantly different at 8 weeks with no correction for multiple comparisons. Nowhere was it stated how many of the 29 patients had pain and how many of those who did have pain responded to the patch and therefore the trial did not provide data that BuTrans had a beneficial effect on pain in patients with dementia. The fact that benefit only became apparent after 2 months, despite daily treatment, also raised questions as to the robustness of the findings.

As the presented data on the effect of the stepped protocol on agitation were not disaggregated by medicine it was impossible to know whether BuTrans had any effect on agitation. This was particularly the case for the 'aggressive behaviour' factor where significant levels were marginal. There was no evidence that BuTrans reduced the need for antipsychotics.

Given the low number of patients taking BuTrans in the study, it was hard to interpret the data on tolerability. However, 4 of the 29 patients dropped out because of side effects including femur fracture, drowsiness and nausea, local reaction to patch, appetite and eating disturbance. Other opiates such as tramadol also had adverse effects in dementia and worsened confusion. Confusion was listed as a common side effect in the BuTrans summary of product characteristics (SPC).

As a clinician who treated agitated patients with dementia, the complainant knew that Husebo *et al* suggested that analgesics might reduce agitation irrespective of whether patients had pain since inclusion criteria did not demand the presence of pain.

The complainant was concerned that the advertisement, in which the wording and the picture clearly indicated aggressive agitation, made a claim that BuTrans had an effect on agitation. Aggressive agitation of the type depicted was a relatively common problem for which doctors often felt compelled to prescribe. However, such patients would not be well served by a treatment which, if effective, took two months to work.

The wording of the promotional material was careful but in the complainant's view it was misleading as it elided the treatment of pain and agitation in a way which was beyond the evidence.

The detailed response from Napp is given below.

The Panel noted that it had been proposed that in some dementia patients the only way that they might be able to express pain was through agitation and aggression and that pain relief might in turn have a beneficial effect on such behaviour. The only clinical study used to support the use of BuTrans to treat pain in dementia patients was Husebo *et al* (2011) which set out to determine whether, over eight weeks, a systematic approach to the treatment of pain could reduce agitation in patients with moderate to severe dementia living in nursing homes. Although further details of the study were published in 2014 by Sandvik *et al* and Husebo *et al*, both postdated the material at issue; the website was approved in November 2013 and the advertisement and detail aid were approved in December 2013.

In Husebo *et al* (2011) nursing home residents were included in the study independent of painful diagnoses, presumed pain or ongoing pain treatment and assigned to a stepwise treatment group or to receive normal management. The ongoing pain treatment could include aspirin or anti-inflammatories provided that patients had been stable on these for four weeks before inclusion into the study. Use of analgesics as needed (other than paracetamol) was also permitted. Clinicians were advised to keep the prescription and dose of psychotropics unchanged where possible. Fifty nine percent of patients in the intervention group had a clinically relevant pain score of ≥3 on a pain scale. The stepwise treatment was step 1, paracetamol (maximum 3g/day), step 2, oral morphine (maximum 20mg/day), step 3, BuTrans (maximum 10µg/hour) and finally, oral pregabalin (maximum 300mg/day). Combination therapy was permitted if needed. The primary outcome measure was agitation as assessed by a nurses' rating questionnaire. Assessment of pain using the pain scale was a secondary outcome measure. Of the 175 patients assigned to the treatment group, 39 (22%) received BuTrans of whom 31 (18%) received the 5µg/hour patch and 8 (5%) received the 10µg/hour patch. The majority of patients (n=120, 69%) received paracetamol. The results showed that agitation was significantly reduced in the intervention group compared with the control group after eight weeks (p<0.001). The differences in pain scores between the control group and the intervention group were statistically significant at weeks 2, 4 and 8 in favour of intervention (p<0.001). The correlation between pain and aggression at week 8 was significant (p=0.01). Husebo *et al* (2011) did not examine between group differences in the intervention group but subsequent analysis by Sandvik *et al*, which was not available when the material at issue was approved, showed that treatment with BuTrans significantly decreased pain scores but not before week 8.

The Panel accepted that the treatment of pain in patients with dementia posed particular problems. The study used to support the use of BuTrans in the treatment of pain in dementia included patients who were presumed to be in pain given that they displayed behaviours such as agitation and aggression; 41% of patients in the intervention group did not have a clinically relevant pain score (≥3) at baseline. The primary outcome measure was not a reduction in pain but a reduction in agitation. Agitation was taken as a marker for pain but patients were not positively diagnosed as having pain. The Panel noted the licensed indication for BuTrans and in that regard it considered that there was no way of knowing if the 39 BuTrans patients included in Husebo *et al* had non-malignant pain of moderate intensity for which an opioid was necessary for obtaining adequate analgesia and that they did not have acute pain. The Panel considered that there was a difference between clinicians reporting clinical research or using a medicine in a particular patient group and a pharmaceutical company using such data to promote its medicine in that patient group. The Panel queried, irrespective of the results of Husebo *et al* (2011), whether the promotion of BuTrans in dementia patients without a positive diagnosis of non-malignant, moderate pain was in accordance with the particulars listed in the BuTrans SPC.

The Panel considered that there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia. The 39 BuTrans patients included in Husebo *et al* (2011) had not been positively diagnosed with non-malignant pain of moderate intensity such that they required an opioid nor was it clear that they did not have acute pain. Analysis of the study results published after the material at issue had been approved showed that the treatment effect of BuTrans was not apparent until week eight of the eight week study. The Panel thus considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine. A breach of the Code was ruled. The Panel considered that claims for the analgesic efficacy of BuTrans in such patients could not be substantiated. A breach of the Code was ruled. These rulings were upheld on appeal. The Appeal Board was particularly concerned about the safety of using BuTrans in this vulnerable patient group given that if they could not verbalise pain, they were unable to express and communicate side-effects. The Panel further considered that within the context of the BuTrans material at issue, the statement 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics' would be assumed to relate to BuTrans. There was no evidence that treatment with BuTrans limited the unnecessary use of antipsychotics. In that regard, the Panel considered that the statement was misleading by implication and could not be substantiated. Breaches of the Code were ruled. These rulings were upheld on appeal.

With regard to the advertisement, the Panel noted its general comments above about the material at issue. The Panel, however, did not consider that the advertisement promoted BuTrans for the treatment of agitation *per se*. On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients. In that regard the Panel did not consider that the advertisement was misleading. No breach of the Code was ruled. This ruling was upheld on appeal.

During its consideration of this case the Panel noted that all of the promotional material included the BuTrans product logo which consisted of the product name in logo type beneath which was stated, 'Buprenorphine Matrix Patch 5µg/h. 10µg/h, 20µg/h'. In that regard the Panel noted that the majority of the 39 BuTrans patients in Husebo *et al* (2011) had been treated with only the low dose patch; 8 patients had had the dose increased to the 10µg/h patch and no-one received the 20µg/h patch.

The Panel was extremely concerned about the material at issue which in its view did not promote the rational use of BuTrans and in that regard it particularly noted the claims in the detail aid and on the website that 'BuTrans makes sense in dementia' and that it was a 'sensible choice' in dementia.

The Panel queried how such a broad, unqualified claim could be made on the basis of treatment of 39 patients. In the Panel's view there was little evidence of the analgesic efficacy of BuTrans in patients with dementia and the Panel noted in particular comments by Husebo *et al* (2011) that it was possible that agitation (the primary outcome measure) declined as a result of patients being sedated following the use of opioid analgesics ie BuTrans or oral morphine (step 2 of the treatment protocol) and comments from Sandvik *et al* that the treatment effect of BuTrans was not apparent until week 8. The Panel also noted that side effects of BuTrans included confusion, agitation and anxiety. The Panel noted its comments above and considered that if its rulings of breaches of the Code were appealed, it would require, in accordance with Paragraph 7.1 of the Constitution and Procedure, the promotional campaign at issue to be suspended pending the final outcome of the case.

Overall, the Panel was concerned that the promotional material at issue was inappropriate. Promoting a medicine in a patient group in whom there was no robust evidence of efficacy was an extremely serious matter. The Panel decided to report Napp to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure for it to decide whether further sanctions were warranted.

The Appeal Board noted the Panel's concerns and rulings including that the Panel had required the material to be suspended pending the final outcome of the case. Given its rulings of breaches, the Appeal Board noted that the material at issue would now have to be withdrawn. The Appeal Board decided, in this instance, to take no further action in relation to the report from the Panel.

A consultant psychiatrist with an NHS Trust, complained about a BuTrans (buprenorphine transdermal patch) advertisement (ref UK/BUTR-13054b) and website (ref UK/BUTR-12036) created by Napp Pharmaceuticals Limited which referred to the difficulty of treating pain in patients with dementia. The complainant also provided a copy of a detail aid (ref UK/BUTR-13057).

BuTrans was indicated for the treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia. BuTrans was not suitable for the treatment of acute pain.

COMPLAINT

The complainant explained that patients with agitation in dementia were more vulnerable to overselling than any other group; fines of over $7 billion had been raised for the over promotion of antipsychotic and antiepileptic medicines by companies for that purpose.

The complainant noted that Napp had placed a full page advertisement for BuTrans in the BMJ which emphasised the medicine's role in dementia. The complainant submitted that Napp was engaged in a promotional campaign to raise awareness of the important and under-recognised problem of pain in dementia.

The complainant stated that agitation and aggression were particularly burdensome for carers. Agitation had multiple causes, one of which was pain. Better pain relief was likely to reduce agitation in dementia and a pain relieving patch made sense because compliance was easier.

The complainant quoted text from the www.butrans.co.uk website as follows along with the list of references:

> 'Pain in dementia is very real but remains significantly under-diagnosed and under-treated (Zwakhalen *et al* 2009, Closs *et al* 2004, Horgas and Tsai 1998 and Reynolds *et al* 2008). Behavioural changes, such as agitation and aggression, may be a patient's only way of showing they're in pain. But these same factors can make pain management even more challenging for family and carers (Cook *et al* 1999 and Sampson and Kitchen 2005).
>
> That's why the once-weekly ***BuTrans*** patch is a sensible choice in dementia.
>
> - It delivers convenient, well-tolerated and consistent relief for seven days, easing the daily pill burden on patients and their carers (BuTrans summary of product characteristics (SPC), Vadivelu and Hines 2008, Napp data on file and Plosker 2011)
> - It can improve treatment compliance compared with oral medication, offering effective long-term management of chronic pain (Plosker 2011 and Gallagher *et al* 2009)
> - As part of a step-wise approach to pain treatment, ***BuTrans*** was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care (Plosker 2011 and Husebo *et al* 2011)
> - Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics (Plosker 2011, Husebo *et al* 2011 and Banerjee 2009))
>
> Explore the website for more information on ***BuTrans***, or learn more about managing pain in dementia by using the external links below:
>
> - **Pain in dementia**
> - **BuTrans is a sensible choice in dementia**
> - **Pain assessment tool.'**

The complainant stated that the following sentences implied that there was evidence to support the use of BuTrans in dementia which was misleading:

> 'As part of a step-wise approach to pain treatment, BuTrans was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care (Plosker 2011 and Husebo *et al* 2011).

Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics.'

The complainant stated that the published evidence about the use of BuTrans in dementia derived from a single trial; various aspects of which had been published (Husebo *et al* 2011, Husebo *et al* 2014, and Sandvik *et al* 2014). In summary, patients were recruited into the trial on the basis that they were agitated, not because they had pain; only 57% were recorded as having clinically relevant pain. BuTrans was used as part of a stepped pain relief protocol in which patients first tried paracetamol, then opiate, then BuTrans, then pregabalin. The majority of patients only took paracetamol. The primary and secondary outcomes were based on reports from those involved in day-to-day care. Whilst attempts to blind the raters were made, no report was made of the success of this effort and carers would have clearly known if someone was treated with a patch or not. Of those allocated to the treatment arm (n=103), only 29 (28%) received a BuTrans patch. Some patients went straight onto the patch because of trouble swallowing but the three papers differed in their account of whether this applied to all of those who started the patch.

Mean scores for pain were not significantly different between control and BuTrans at week 2 or week 4 but were significantly different at 8 weeks with no correction for multiple comparisons. Nowhere in the publications was it stated how many of the 29 patients had pain and how many of those who did have pain responded to the patch and therefore the trial did not provide data that BuTrans had a beneficial effect on pain in patients with dementia. The fact that benefit only became apparent after 2 months, despite daily treatment, also raised questions as to the robustness of the findings.

As the presented data on the effect of the stepped protocol on agitation were not disaggregated by medicine it was impossible to know whether BuTrans had any effect on agitation. This was particularly the case for the 'aggressive behaviour' factor where significant levels were marginal. There was no evidence that BuTrans reduced the need for antipsychotics.

Given the low number of patients taking BuTrans in the study, it was hard to interpret the data on tolerability. However, 4 of the 29 patients dropped out because of side effects including femur fracture, drowsiness and nausea, local reaction to patch, appetite and eating disturbance. Other opiates such as tramadol also have adverse effects in dementia and worsen confusion. The complainant noted that confusion was listed as a common side effect in the BuTrans SPC.

As a clinician who treated agitated patients with dementia, the complainant knew that following wide publicity at the time, Husebo *et al* suggested that analgesics might reduce agitation irrespective of whether patients had pain since inclusion criteria did not demand the presence of pain.

The complainant stated that he/she had complained because his/her first impression of the advertisement, in which the wording and the picture clearly indicated aggressive agitation, was that it made a claim that BuTrans had an effect on agitation. Aggressive agitation of the type depicted was a relatively common problem for which doctors often felt compelled to prescribe. However, such patients would not be well served by a treatment which, if effective, took two months to work.

The wording of the promotional material was careful but in the complainant's view it was misleading as it elided the treatment of pain and agitation in a way which was beyond the evidence.

When writing to Napp, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

Napp submitted that it took compliance very seriously and was naturally disappointed to learn that any of its materials should be the subject of a complaint from a health professional.

Napp submitted that it had taken into consideration the complainant's comments, although it was difficult to identify the precise focus of the complaint; with respect to the Code Napp considered that there were two promotional items at issue. The first was the BuTrans advertisement in the BMJ and the second was the BuTrans pain in dementia webpage.

Napp submitted that it was established that pain in patients who suffered from dementia was an under recognised and undertreated condition:

- People with dementia were as likely to feel pain to the same extent as individuals without dementia, but might have lost the verbal skills necessary to express and communicate their pain (Herr 2006). As a result it could be difficult for carers to identify whether patients were in pain. Indeed people with dementia took fewer analgesics and reported less pain compared with their non-cognitively impaired peers (Reynolds *et al* 2008, Achterberg *et al* 2013 and Pieper *et al* 2013).
- A 2009 report, commissioned by the Department of Health (DoH), highlighted the overuse of antipsychotics to treat behavioural and psychological disturbances (such as agitation and aggression) in dementia. The report gave recommendations to reduce their use given that it was estimated that annually they caused more than 1,620 cerebrovascular adverse events and 1,800 deaths (Banerjee 2009).
- The assessment of pain in dementia patients was particularly challenging and behavioural pain scales had been specifically developed to assess pain in dementia patients. Three behaviours, 'pain noises', 'facial expression' and 'defence' behaviours, were specifically examined in the MOBID-2 pain scale (Husebo *et al* 2011, Husebo *et al* 2014 and Sandvik *et al* 2014). Facial expression was used to denote movement caused by pain,

expressed by the words: grimacing, frowning, tightening mouth and closing eyes.

- The National Institute for Health and Care Excellence (NICE) Dementia Guidelines, the 2009 DoH report on the use of antipsychotics in dementia and current guidelines from the Alzheimer's Society recommended that the first line management of behavioural and psychological disturbances in dementia should be a detailed assessment to identify any treatable causes such as pain. Indicators for pain in a person with dementia included either withdrawn or disturbed behaviour, which could include agitation and aggression.

Napp submitted that the treatment of pain in dementia had been subject to several reviews which concluded that the 'available evidence suggests that (pain) interventions targeting behaviour, and (behavioural) interventions targeting pain are effective in reducing pain and behavioural symptoms in dementia' (Achterberg *et al* 2013 and Pieper *et al* 2013). This included a study (discussed by the complainant) that demonstrated the treatment of pain in dementia could reduce behavioural symptoms including agitation and aggression (Husebo *et al* 2011).

Husebo *et al* (2011) was published in the BMJ and further data analyses from this study was published in 2014 (Husebo *et al* and Sandvik *et al*).

- The study was a cluster randomised controlled trial published in a recognised peer-reviewed journal and used a well validated tool (Cohen-Mansfield Agitation Inventory) to evaluate agitation in dementia patients.
- The objective of this study was to determine whether a systematic approach to the individualised treatment of pain could reduce agitation in people with moderate to severe dementia living in nursing homes.
- There were four steps in the pain management protocol: 1, paracetamol (maximum 3g/day), 2, morphine (maximum 20 mg/day), 3, BuTrans (maximum 10 micrograms/hour) and 4, pregabalin (maximum 300 mg/day).
- The study demonstrated that a step-wise approach to pain management in dementia patients significantly improved their pain and behavioural disturbances, including agitation and aggression.

Napp submitted that BuTrans was a long-lasting analgesic in the form of a transdermal patch containing the opioid buprenorphine, available in three strengths (5, 10 & 20 micrograms/hour) and provided pain relief for up to seven days. BuTrans was licensed for the treatment of non-malignant pain of moderate intensity when an opioid was necessary for obtaining adequate analgesia and its use was well established in the UK since launch in 2005.

Dementia patients were often elderly and suffered from a number of chronic painful co-morbidities (e.g. musculoskeletal pain, old fractures and arthritis). BuTrans was therefore an appropriate option for treating pain in this patient group because:

- The prolonged release formulation provided consistent analgesia for up to seven days
- BuTrans did not require dose adjustment in the elderly nor in patients with severe renal impairment.
- A patch formulation could reduce the pill burden on patients and was a convenient alternative for those who had difficulty swallowing (Plosker 2011).

In light of the background provided above, the focus of the materials at issue was to:

- highlight the difficulty in assessing pain in patients with dementia
- raise awareness of the common signs that could indicate pain (e.g. agitation and aggression).
- demonstrate BuTrans was an appropriate option to treat chronic pain in such patients.

Having considered the complaint about the BMJ advertisement in terms of Clauses 7.2 and 7.4, Napp disagreed with the allegation that it was misleading and submitted that the claims could be substantiated.

Napp submitted that the advertisement did not state that BuTrans had an effect on agitation. The imagery and accompanying text combined, placed a clear and explicit emphasis on pain management in dementia and in this respect BuTrans was a well-established analgesic, licensed for the treatment of moderate pain.

The supporting rationale for Napp's position was:

- The complainant had recognised in his/her opening paragraphs that pain in dementia was an 'important and under-recognised problem'. As acknowledged in the NICE guidelines on dementia (NICE CG42), the DoH report (Bannerjee 2009) and the Alzheimer's Society Report (Alzheimer's Society 2011) there was an established link between pain and behavioural disturbances in dementia, because these patients often found it hard to express themselves verbally. This could manifest itself in a number of ways including facial expressions denoting agitated, aggressive or challenging behaviour.
- The focus of the advertisement was on the management of pain in line with Napp's licensed indication, which stated that BuTrans was indicated for the treatment of moderate pain.
- The advertisement was intended to portray the facial expression of a patient in pain who, because of his dementia, was only able to express this through agitation and verbal aggression. Feedback from health professionals, including GPs, geriatricians and nurses during the development of this material was that the imagery was memorable, evocative and led to immediate patient identification for many.
- The advertisement text made no claim for BuTrans in the treatment of agitation in dementia patients. The emphasis of the text was on pain management; 'Agitation and aggression' was used only once at the start but specifically in the context of describing how patients with dementia could struggle to express that they were in pain.

In contrast 'pain' or 'analgesia' were used five times to emphasise that the advertisement was about pain management.
- The prominent strap line 'Dementia hurts enough without pain' underneath the image further stated the advertisement's focus was on pain management and not on agitation.
- The advertisement had comprehensive information for prescribers to be well informed about the use of BuTrans in the treatment of pain as clearly stated in the prescribing information.

The text and image taken as a whole clearly focussed on the use of BuTrans for pain management and not for agitation. The use and efficacy of BuTrans for the treatment of pain was well established and capable of substantiation. Therefore, Napp disagreed that there had been a breach of Clause 7.2 or 7.4.

With regard to the complaint about the BuTrans pain in dementia webpage in terms of Clauses 7.2 and 7.4, Napp disagreed with the allegation that the sentence referred to by the complainant, 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics' was misleading and submitted that the claims were capable of substantiation.

Napp submitted that it had not stated that BuTrans had supporting evidence for treating agitation and aggression in dementia.

The supporting rationale for Napp's position was:

- That it clearly stated that a step-wise approach to pain management was carried out (using various analgesics) and that BuTrans, which was licensed for moderate pain, was a part of that approach. Napp submitted that it did not claim that BuTrans directly improved agitation and aggression in dementia, nor did it claim that BuTrans alone was responsible for the observed finding.
- Therefore, as suggested by the complainant, the wording was indeed carefully chosen to reflect in the first instance that a step-wise approach to pain management was used, whilst secondly reflecting that BuTrans was part of (i.e. 'was associated with') the step-wise approach to the management of pain.
- Furthermore, the context of the webpage as a whole was clearly about the challenge of identifying and treating pain in patients with dementia, and that BuTrans was an appropriate choice for treating that pain.

Based on the above Napp disagreed that it had been misleading about the use of BuTrans in the treatment of agitation and aggression in dementia.

- Napp noted that the complainant highlighted Husebo *et al* (2011) as a key piece of evidence, from which he/she alleged that Napp had made misleading claims for BuTrans with respect to agitation and aggression. As discussed above, this study was well designed and published in a peer reviewed journal (BMJ).
- The study demonstrated that following a step-wise approach to pain management in dementia patients could significantly improve pain and behavioural disturbances, including agitation and aggression. BuTrans, which was licensed in the treatment of moderate pain was used at step three.
- The complainant stated that 28 patients received BuTrans, however 37 patients were treated with BuTrans (Husebo *et al* 2011).

Napp submitted that it had not stated that BuTrans had supporting evidence for treating agitation and aggression in dementia. Napp clearly stated that a step-wise approach to pain management was carried out, that BuTrans (which was licensed for moderate pain) was a part of this approach, and that such an approach reduced agitation and aggression, all of which could be substantiated.

Napp therefore denied a breach of Clause 7.2 or 7.4.

Having considered the complaint about the BuTrans dementia webpage in terms of Clause 7.2 and 7.4, Napp disagreed with the allegation that the sentence on the webpage, 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics' was misleading and believed that the claims made could be substantiated.

The supporting rationale for Napp's position was as follows:

- Napp submitted that it had not stated that BuTrans was associated with reduced antipsychotic usage. BuTrans was not mentioned in the sentence. Therefore, it denied that it had claimed that use of BuTrans to treat pain in dementia could limit unnecessary antipsychotic usage.
- In the wider context of the webpage text, it was clear that Napp had focussed on the appropriate management of pain in patients with dementia. Therefore, Napp submitted that it had not misled about the effect of BuTrans on antipsychotics.
- Napp submitted that as stated above, it was an established problem that antipsychotics were overused to treat behavioural and psychological disturbances, including agitation and aggression, in dementia (Bannerjee 2009). This overuse of antipsychotics was estimated to cause more than 1,620 cerebrovascular adverse events and 1,800 deaths per year (Bannerjee 2009).
- It was therefore recommended that the first line management of behavioural and psychological disturbance should be a detailed assessment to identify any treatable causes, which included pain, before the use of antipsychotics was considered (Bannerjee 2009, NICE CG42, Alzheimer's Society 2011).
- It was clear from the clinical guidelines that if improved treatment approaches to pain could reduce pain-related behavioural disturbances (Husebo *et al* 2011), then this could reduce the need for unnecessary antipsychotics.

Napp submitted that in light of the above clinical guidelines, the sentence 'Effectively managing pain in dementia can help reduce pain-related

behavioural disturbances, limiting unnecessary use of antipsychotics' could be substantiated. Therefore, based on the above, Napp denied a breach of Clause 7.2 or 7.4.

Finally, Napp noted that the complainant stated in his/her introductory paragraphs that Napp 'was engaged on a promotional campaign to raise awareness of the important and under-recognised problem of pain in dementia' and that 'agitation and aggression were particularly burdensome for carers. Agitation had multiple causes, one of which was pain. Better pain relief was likely to reduce agitation in dementia and a pain relieving patch made sense because compliance was easier'. In this respect the complainant had provided an accurate description of the intent and purpose of the content of the advertisement and web page in question.

PANEL RULING

The Panel noted that BuTrans was indicated for the treatment of non-malignant pain of moderate intensity when an opioid was necessary for obtaining adequate analgesia. BuTrans was not suitable for the treatment of acute pain.

The Panel noted that Napp had confined the comments in its response to the advertisement and the web page. The complainant, however, had provided a copy of the detail aid which in turn had been provided to Napp. In the Panel's view the detail aid was within the scope of the complaint.

The Panel noted that it had been proposed that in some dementia patients with impaired language and abstract thinking, the only way that they might be able to express pain was through agitation and aggression and that pain relief might in turn have a beneficial effect on such behaviour. The only clinical study used to support the use of BuTrans to treat pain in dementia patients was Husebo *et al* (2011) which set out to determine whether, over eight weeks, a systematic approach to the treatment of pain could reduce agitation in patients with moderate to severe dementia living in nursing homes. Although further details of the study were published in 2014 by Sandvik *et al* and Husebo *et al*, both postdated the material at issue; the website was approved in November 2013 and the advertisement and detail aid were approved in December 2013.

In Husebo *et al* (2011) nursing home residents were included in the study independent of painful diagnoses, presumed pain or ongoing pain treatment and assigned to a stepwise treatment group or to receive normal management. The ongoing pain treatment could include aspirin or anti-inflammatories provided that patients had been stable on these for four weeks before inclusion into the study. Use of analgesics as needed (other than paracetamol) was also permitted. Clinicians were advised to keep the prescription and dose of psychotropics unchanged where possible. Fifty nine percent of patients in the intervention group had a clinically relevant pain score of ≥3 on the mobilization-observation-behaviour-intensity-dementia-2 (MOBID-2) pain scale at baseline. MOBID-2 was an observational pain scale which assessed pain intensity based upon a patient's immediate pain behaviour such as vocalisation, facial expression and use of defensive body positions. The stepwise treatment was step 1, paracetamol (maximum 3g/day), step 2, oral morphine (maximum 20mg/day), step 3, BuTrans (maximum 10µg/hour) and finally, oral pregabalin (maximum 300mg/day). Combination therapy was permitted if needed. The primary outcome measure was agitation as assessed by a nurses' rating questionnaire. Assessment of pain using the MOBID-2 pain scale was a secondary outcome measure. Of the 175 patients assigned to the treatment group, 39 (22%) received BuTrans of whom 31 (18%) received the 5µg/hour patch and 8 (5%) received the 10µg/hour patch. The majority of patients (n=120, 69%) received paracetamol. The results showed that agitation was significantly reduced in the intervention group compared with the control group after eight weeks ($p<0.001$). The differences in MOBID-2 scores between the control group and the intervention group were statistically significant at weeks 2, 4 and 8 in favour of intervention ($p<0.001$). The correlation between pain and aggression at week 8 was significant ($p=0.01$). Husebo *et al* (2011) did not examine between group differences in the intervention group but subsequent analysis by Sandvik *et al*, which was not available when the material at issue was approved, showed that treatment with BuTrans significantly decreased MOBID-2 pain scores but not before week 8.

The Panel accepted that the treatment of pain in patients with dementia posed particular problems both for the patient and the care givers. The study used to support the use of BuTrans in the treatment of pain in dementia included patients who were presumed to be in pain given that they displayed behaviours such as agitation and aggression; 41% of patients in the intervention group did not have a clinically relevant score (≥3) on the MOBID-2 pain scale at baseline. The primary outcome measure was not a reduction in pain but a reduction in agitation. Agitation was taken as a marker for pain but patients were not positively diagnosed as having pain. The Panel noted the licensed indication for BuTrans and in that regard it considered that there was no way of knowing if the 39 BuTrans patients included in Husebo *et al* had non-malignant pain of moderate intensity for which an opioid was necessary for obtaining adequate analgesia and that they did not have acute pain. The Panel considered that there was a difference between clinicians reporting clinical research or using a medicine in a particular patient group and a pharmaceutical company using such data to promote its medicine in that patient group. The Panel queried, irrespective of the results of Husebo *et al* (2011), whether the promotion of BuTrans in dementia patients without a positive diagnosis of non-malignant, moderate pain was in accordance with the particulars listed in the BuTrans SPC.

The Panel noted that the complainant had stated that the following sentences on the BuTrans website implied that there was evidence to support the use of BuTrans in dementia which was misleading:

> 'As part of a step-wise approach to pain treatment, BuTrans was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care (Plosker 2011 and Husebo *et al* 2011)
>
> Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics.'

The Panel considered that there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia. The 39 BuTrans patients included in Husebo *et al* (2011) had not been positively diagnosed with non-malignant pain of moderate intensity such that they required an opioid nor was it clear that they did not have acute pain. Analysis of the study results published after the material at issue had been approved showed that the treatment effect of BuTrans was not apparent until week eight of the eight week study. The Panel thus considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine. A breach of Clause 7.2 was ruled. The Panel considered that claims for the analgesic efficacy of BuTrans in such patients could not be substantiated. A breach of Clause 7.4 was ruled. These rulings were appealed. The Panel further considered that within the context of the BuTrans material at issue, the statement 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics' would be assumed to relate to BuTrans. There was no evidence that treatment with BuTrans limited the unnecessary use of antipsychotics. In that regard, the Panel considered that the statement was misleading by implication and could not be substantiated. A breach of Clauses 7.2 and 7.4 was ruled. These rulings were appealed.

With regard to the advertisement, the Panel noted its general comments above about the material at issue. The Panel, however, did not consider that the advertisement promoted BuTrans for the treatment of agitation *per se*. On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients. In that regard the Panel did not consider that the advertisement was misleading. No breach of Clause 7.2 was ruled. This ruling was appealed.

During its consideration of this case the Panel noted that all of the promotional material included the BuTrans product logo which consisted of the product name in logo type beneath which was stated, 'Buprenorphine Matrix Patch 5µg/h. 10µg/h, 20µg/h'. In that regard the Panel noted that the majority of the 39 BuTrans patients in Husebo *et al* (2011) had been treated with only the low dose patch; 8 patients had had the dose increased to the 10µg/h patch and no-one received the 20µg/h patch.

The Panel was extremely concerned about the material at issue which in its view did not promote the rational use of BuTrans and in that regard it particularly noted the claims in the detail aid and on the website that 'BuTrans makes sense in dementia' and that it was a 'sensible choice' in dementia. The Panel queried how such a broad, unqualified claim could be made on the basis of treatment of 39 patients. In the Panel's view there was little evidence of the analgesic efficacy of BuTrans in patients with dementia and the Panel noted in particular comments by Husebo *et al* (2011) that it was possible that agitation (the primary outcome measure) declined as a result of patients being sedated following the use of opioid analgesics ie BuTrans or oral morphine (step 2 of the treatment protocol). However the authors noted that only 25.6% of patients were treated with a sedative agent and that only 3 were excluded because of drowsiness or nausea. Sandvik *et al* reported that the treatment effect of BuTrans was not apparent until week 8 and also noted that due to the metabolic pathway of buprenorphine, careful monitoring was required in patients with hepatic impairment, and this was an important consideration when prescribing to patients with dementia. The Panel noted that a common (≥1/100, <1/10) side effect listed in the BuTrans SPC was confusion, uncommon (≥1/1000, <1/100) side effects included agitation and anxiety and rarely (≥1/10,000, <1/1000) the medicine could cause psychotic disorders. The Panel noted its comments above and considered that if its rulings of breaches of the Code were appealed, it would require, in accordance with Paragraph 7.1 of the Constitution and Procedure, the promotional campaign at issue to be suspended pending the final outcome of the case.

Overall, the Panel was concerned that the promotional material at issue was inappropriate as discussed above. Promoting a medicine in a patient group in whom there was no robust evidence of efficacy was an extremely serious matter. The Panel decided to report Napp to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure for it to decide whether further sanctions were warranted.

APPEAL FROM THE COMPLAINANT

The complainant appealed the Panel's ruling of no breach of Clause 7.2 concerning the advertisement and noted that the Panel's comments also suggested that there might have been a breach of Clause 3.2.

The complainant noted that Clause 7.2 stated:

> 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis.
>
> Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine.'

The complainant gave the following as his grounds for appeal:

1 The complainant disagreed with Napp's submission that '... the advertisement did not state that BuTrans had an effect on agitation. The imagery and accompanying text combined placed a clear and explicit emphasis on pain management in dementia ...'. The Panel ruled that it 'did not consider that the advertisement promoted BuTrans for the treatment of agitation *per se*'. However, the devil here was in the '*per se*'. The complainant alleged that the words and the image conflicted; the words talked about pain but the image depicted aggression, not pain.

a) Indeed, Napp clearly stated that the image depicted agitation and aggression: 'The advertisement was intended to portray ... agitation and verbal aggression'. (The omitted words here were 'the facial expression of a patient in pain who because of his dementia, was only able to express this through'). Napp also submitted that feedback from professionals was that the '... imagery was memorable, evocative and led to immediate patient identification for many'. The complainant agreed with this and alleged that this was exactly the problem. Most agitation and aggression was nothing to do with pain (as evidenced by the fact that only 41% of those in the study had significant clinical pain). A less misleading image would make clear the primary role of pain rather than just depicting agitation/aggression.

b) The complainant alleged that it might sometimes be reasonable for images to depict downstream symptomatic benefits of a primary proven effect. However, there were two problems with this. Firstly, this was different from depicting an indication which was not part of the licence. This was the fundamental error that led Pfizer and others to incur such huge fines when they promoted their medicines for agitation and psychosis in dementia. (Incidentally, the quality of the evidence for a benefit of antipsychotics on agitation in dementia was higher than that for BuTrans). Secondly, the primary effect was not proven: as the Panel stated, '... there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia'.

2 The complainant alleged that there was internal inconsistency in the ruling because 'The Panel ruled the website in breach because it considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine'. However, exactly the same materials pertained to the BMJ advertisement. Similar wording, which was criticised by the Panel in respect of the website, was used in the advertisement; including the notion that it 'makes sense' ('That's why BuTrans transdermal patches make sense').

3 The complainant noted the Panel's statement that 'On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'. However, the Panel also 'considered that there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia'. It also 'considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine'. This might, therefore, amount to a breach of Clause 3.2 ('The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics') as well as Clause 7.4. This possibility did not appear to have been considered.

4 The complainant alleged that the number of patients treated with BuTrans in the study was difficult to ascertain. Napp referred to 37. Sandvik *et al* stated: 'Step 3, the buprenorphine transdermal patch, was administered to 29 patients (17.7%), and the buprenorphine dosage was increased in an additional eight participants. In total, 37 participants were treated with buprenorphine transdermal patch, of whom 9 received the patch alone, with no other medication, due to swallowing issues'. Husebo *et al* stated: 'Thirty one participants (18%) received step 3 (buprenorphine transdermal patch), and in addition eight participants (5%) the dosage was increased'. This suggested that 8 patients in the intervention arm (ie 22%) were already taking buprenorphine before the study started. It was not known how many patients in the control arm were already taking buprenorphine.

5 The complainant alleged that whilst the intent and purpose of the advertisement was understandable, the claims went beyond the evidence and were misleading.

COMMENTS FROM NAPP

Napp submitted that the specific grounds stated by the complainant for the appeal had been addressed in its previous submissions hence it referred to its previous submissions.

Napp's responded to the complainant's appeal using the same numbering as above.

1/1a Napp noted the allegation that the words and image conflicted. The words talked about pain but the image was not one of pain. It depicted aggression, not pain. Napp referred to its response to the complainant and its appeal on this point.

Napp submitted that the link between pain and aggression was very clear from the available literature (ie not just Husebo *et al*) but for the avoidance of any doubt, it had never claimed that aggression in patients with dementia was caused exclusively by pain. The advertisement was intended to bring to the attention of clinicians the need to consider pain in patients with dementia who became agitated. Pain

scales developed for the assessment of pain in dementia patients with severe cognitive impairment (who were unable to adequately verbalise their pain) included behavioural assessments. This again highlighted that a behavioural change might be due to pain as part of a differential diagnosis.

Napp noted that a complainant had the burden of proving his/her complaint on the balance of probabilities, as stated in the introduction of the Constitution and Procedure. The Panel ruled '... On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'. In that regard, the Panel did not consider the advertisement was misleading. Napp firmly maintained that the combination of text and imagery in the advertisement was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine, as required under Clause 7.2.

1b Napp submitted that the complainant's comment about imagery had been dealt with in its response in the above.

With respect to the complainant's comments about the therapeutic indication of BuTrans, Napp referred to its appeal.

2 Napp agreed that there was a potential inconsistency in the Panel's rulings. However, Napp now understood that the Panel ruled the advertisement not to be in breach of Clause 7.2 on the specific point about being misleading as to the promotion of BuTrans in agitation, but its general comments about the evidence base in pain made in the context of the webpage applied equally to the advertisement. Napp had addressed this in its appeal and in the above.

3 Napp referred to its response to point 1a above. Napp had been asked by the PMCPA not to respond to a complaint under Clause 3.2 as it was not within the scope of the complaint.

4 Whilst Napp agreed that the number of dementia patients treated with BuTrans was difficult to ascertain depending on which paper was considered, this was 39 patients in Husebo *et al* (2011) which was cited in the advertisement: 'Thirty one participants (18%) received step 3 (buprenorphine transdermal patch), and in addition eight participants (5%) the dosage was increased'. However, Napp was unclear as to the specific relevance of this to the complainant's appeal.

Napp noted that five references were cited in the BMJ advertisement and not solely the Husebo *et al* (reference 4). These references taken together when considering the advertisement supported the claims:

- Reference 1 (Cook *et al* 1999) 'Pain among people with cognitive impairment can also lead to increased care demand, as cognitive impairment is associated with the presence of depression and challenging behaviours, including aggression and '"disruptive" vocalizations'
- Reference 2 the BuTrans SPC, with licence information for clinicians
- Reference 3 (Plosker 2011) a review article of BuTrans for treatment of pain: 'As noted in section 3.3 [of this review article], the pharmacokinetic profile of buprenorphine is not significantly altered by renal impairment or advanced age, and dosage adjustments of transdermal buprenorphine are not required in these patient populations (section 6 [of this review article]). On the basis of these properties, a recent European consensus statement recommended transdermal buprenorphine as a first-line opioid for chronic pain in elderly patients'
- Reference 5 (Vadivelu *et al* 2008) a review article of the management of chronic pain in the elderly using transdermal buprenorphine including BuTrans: described the advantages and disadvantages of transdermal buprenorphine, including patients with dementia.

5 Napp submitted that it was rational and clinically appropriate to promote BuTrans for the treatment of moderate, chronic pain in dementia patients. Napp noted that the complainant believed that the intent and purpose of the advertisement was understandable. This intent was clearly conveyed in the advertisement, since the text and image taken as a whole clearly focussed on the use of BuTrans for pain management and not for agitation. Napp disagreed with the complainant's assertion that the claims went beyond the evidence and that they were misleading.

To conclude, Napp took compliance very seriously and felt strongly that the BuTrans advertisement was appropriate given its response.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant noted Napp's submission that the reasonable impression to be obtained from the materials was that the advertisement made claims for the use of BuTrans in the treatment of pain (and not for the direct treatment of agitation or aggression). The Panel had noted that 'On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'.

The complainant stated that his appeal against this ruling was on two grounds: firstly, if one accepted that this was a promotion for pain in dementia, this claim was not substantiated at the time, and had not been subsequently substantiated and secondly, clinicians who dealt with aggressive patients would strongly recognise the image and would think that it was promoting for aggression.

1 Promotion of BuTrans for pain

The complainant noted that Napp had argued that it was not necessary to provide evidence of benefit in the specific instance of pain being discussed (ie in dementia) on the grounds that it fell within its current authorization. 'Pain in patients who suffer from dementia represents a population with chronic pain and was therefore within our licensed indication. Dementia is a co-morbidity to chronic pain rather than dementia being a specific pain syndrome'.

However, the complainant alleged that there was a clear difference between the marketing authorization and whether an advertisement was misleading. If there was an overwhelming volume of high quality evidence that, in a particular population with pain, BuTrans had no beneficial effect, then promotion of BuTrans for use specifically in that population would be misleading. There must be a point at which the promotion was misleading if it was not supported by the evidence – that was, if it could not be substantiated.

The complainant alleged that a clinician reading the advertisement would reasonably assume that given the focus on dementia, there was relevant evidence for benefit on pain in patients with dementia; and that the studies of dementia patients which were cited supported that contention.

The complainant agreed with Napp that the different rulings on the advertisement and on the other material resulted in a degree of internal inconsistency. In particular, the issue of whether the material could be substantiated was broadly similar in the advertisement/website since it was based on the same evidence.

The complainant shared the Panel's view that '… there was no robust evidence to support the use of BuTrans in the treatment of pain in patients with dementia.' and that '… the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine'.

The complainant alleged that when the advertisement was approved, the published evidence was such that even a diligent clinician could not access any evidence relating to the benefit of BuTrans on pain in dementia. The only study with any data on BuTrans for patients with dementia was Husebo *et al* (2011). The inclusion criteria were related to agitation and not to pain. Many patients did not have significant pain on the MOBID-2 pain scale (which assessed pain which was not verbally expressed). There was no separation of the data on pain into those with or without clinically significant pain. Nor was data about paracetamol disaggregated from that for BuTrans.

The complainant noted that following the publication of further data in Husebo *et al* (2014) and Sandvik *et al* (2014), it was now known that BuTrans had no benefit on pain before 8 weeks, despite the fact that buprenorphine levels reached a steady state within a few days. This, coupled with the absence of pain data on patients who had not already been receiving BuTrans, the small sample size of 29 who were not taking BuTrans before the trial started, and the lack of control for multiple comparisons, meant that the assertion in Sandvik *et al* (2014) of a demonstration of efficacy on pain at 8 weeks did not, even now, have a 'sound statistical basis' (Figure 5 from Sandvik *et al* 2014). Even if the effect at week 8 was real, it was hard to see how the effect of a patch, which resulted in plateau levels within a few days, was delayed for nearly 2 months.

The complainant stated that the references cited in support of a promotion must support the point being made in the promotion if the advertisement was not to be 'misleading by implication'. Husebo *et al* (2011) was cited throughout the promotional campaign including the advertisement (as reference 4).

The complainant alleged that if the campaign was intended to increase awareness of the possibility that treating pain might reduce agitation, then the above graph implied that paracetamol, not BuTrans, should have been the suggested treatment option (notwithstanding Buffum *et al* 2004 – see below). The American Geriatric Society recommended paracetamol as first line treatment for pain in dementia.

2 Promotion of BuTrans for agitation

The complainant alleged that Napp had denied that the advertisement promoted BuTrans for agitation. However, Napp explicitly stated that the image was intended to convey aggressive agitation: 'The advertisement was intended to portray ... agitation and verbal aggression'. (The omitted words were 'the facial expression of a patient in pain who because of his dementia, was only able to express this through').

The complainant stated that the key point was that, for practising clinicians leafing through the BMJ, the impact of the striking image and the aggression conveyed by the strapline 'You can stick your tablets' overwhelmed the pain message. Clinicians would assume that the image depicted the sort of patient for whom the medicine was being promoted. It was difficult to avoid the implication that aggression was the target of the treatment, especially on a cursory reading. This impression was particularly heightened by the phrase '… easing the burden on patients **and their carer too**' (emphasis added). The effect of agitated behaviour, and aggression in particular, on carer burden was a major concern for prescribers. The impression that the target was agitation was reinforced by reference in the sales aid and website to the potential for reducing antipsychotic use.

The complainant alleged that there was no evidence from Husebo *et al* (2011), Husebo *et al* (2014), Sandvik *et al* or indeed any other trial, to show that opiates had a benefit on agitation in dementia. Whilst Husebo *et al* (2011) showed that

stepped analgesia might be of benefit, no data was presented to show that the introduction or increase of BuTrans reduced agitation any more than paracetamol. Therefore, if the image and words together were considered to promote BuTrans for agitation, they did not clearly reflect the evidence, misled by implication and were not substantiable. If the promotion was merely about compliance in dementia, or compliance in pain in dementia, it did not need to include such a striking image of aggression.

Thus, the complainant alleged that even if the image and words together were not considered to promote BuTrans for agitation, the image and words represented an undue emphasis on agitation. They also made the advertisement ambiguous as to the indication for which BuTrans was promoted.

APPEAL FROM NAPP

Napp confirmed that it had suspended the campaign materials pending the outcome of the appeal.

Napp submitted that was proud to be a leader in pain management and took the responsibility of promoting its analgesics very seriously to ensure clinicians were best informed to prescribe them appropriately. During the development of the campaign Napp was advised by a panel of health experts in both pain management and dementia. Napp refuted the Panel's rulings and firmly believed that it was appropriate to promote BuTrans for the treatment of pain in dementia.

Napp reiterated that it understood that the complaint was focussed on two materials – specifically the BMJ advertisement and the pain in dementia webpage – and Napp was asked to consider the complaint in terms of Clauses 7.2 and 7.4.

Napp interpreted the complaint as follows:

The BMJ advertisement was misleading because it claimed that BuTrans had a direct effect on agitation, and this was not capable of substantiation.

The pain in dementia webpage was misleading because, again, it claimed that BuTrans had a direct effect on agitation and aggression and that its use could lead to reduced use of antipsychotics, and neither of these were capable of substantiation. The complaint referred to the following two statements on the webpage:

> 'As part of a step-wise approach to pain treatment, BuTrans was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care (Husebo *et al* 2011).'
>
> 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics.'

Napp denied that it was misleading in the manner described above. As previously explained the intent behind, and the reasonable impression to be obtained from the materials was that:

- The advertisement made claims for the use of BuTrans in the treatment of pain (and not for the direct treatment of agitation or aggression)
- The webpage statement which referenced Husebo *et al* (2011) was a general statement focused on the step-wise management of pain (for which BuTrans was an appropriate option)
- The webpage statement about antipsychotic use was again a general statement focussed on the potential reduction in the amount of antipsychotic prescriptions if pain was properly managed and BuTrans itself was not claimed to cause a reduction in antipsychotic use. Furthermore, Napp submitted that the claims could be substantiated. Napp thus denied breaches of Clauses 7.2 and 7.4.

1 BMJ advertisement

Napp noted that no breach of Clause 7.2 was ruled. The Panel '…did not consider that the advertisement promoted BuTrans for the treatment of agitation *per se*. On balance, it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'. The Panel did not comment in relation to Clause 7.4 but Napp noted the broader comments made about the promotion of BuTrans in the treatment of pain in patients with dementia in point 3 below.

2 Pain in dementia webpage

a) 'As part of a step-wise approach to pain treatment, BuTrans was associated with reduced agitation and aggression in cognitively impaired nursing home residents, compared with those receiving their usual treatment and care'.

Napp noted that the Panel ruled a breach of Clauses 7.2 and 7.4. However, the Panel´s ruling of misleading was not on the basis that Napp had claimed that BuTrans had a direct effect on agitation and aggression, as Napp had interpreted the complaint. Rather, the Panel stated that 'use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine' and 'the analgesic efficacy of BuTrans in such patients could not be substantiated'.

b) 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics'.

Napp noted that the Panel ruled breaches of Clauses 7.2 and 7.4. The Panel considered that '… within the context of the BuTrans material at issue [the statement above] would be assumed to relate to BuTrans', 'there was no evidence that treatment with BuTrans limited the unnecessary use of antipsychotics' and 'the statement was misleading by implication and could not be substantiated'.

3 Report to the Appeal Board

Napp noted that the Panel had made a number of general comments about the materials used in the campaign. The Panel considered that the BuTrans sales aid was part of the original complaint. This material was duly considered in this response in light of the general comments made by the Panel below. However, Napp submitted that there was no specific discussion or complaint about the sales aid in the complaint.

Napp noted that the Panel: stated in its ruling that the materials at issue 'did not promote the rational use of BuTrans'; queried how the broad, unqualified claims 'BuTrans makes sense in dementia' and BuTrans was a 'sensible choice' in dementia could be made on the basis of treatment of 39 patients and was concerned that the promotional material at issue was 'inappropriate' and that 'promoting a medicine in a patient group in whom there was no robust evidence of efficacy was an extremely serious matter'.

Napp submitted that as it had been reported to the Appeal Board and given the seriousness of the allegations made in relation to the 'pain in dementia' campaign as a whole, its response was in two parts. Part 1 dealt with Panel ruling 1 and the reasons for the report to the Appeal Board whilst Part 2 dealt with Panel ruling 2a) and ruling 2b) (defined above).

Background to BuTrans

Napp submitted that BuTrans was a prescription only analgesic which contained the active medicine buprenorphine within a transdermal patch. When attached to the upper body, the medicine slowly diffused from the patch, across the skin and into the bloodstream where it exerted its analgesic affect in the central nervous system. BuTrans was available at three different strengths (5, 10 and 20micrograms/hour) classified by how much dose was delivered each hour. BuTrans provided pain relief for up to seven days and was the only seven-day patch of its kind currently available. BuTrans was licensed for the 'treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia. BuTrans was not suitable for the treatment of acute pain' (BuTrans SPC) and its use was well established in the UK since launch in 2005.

Part 1: Panel rulings 1, 2 and the report to the Appeal Board

Napp noted that the Panel had ruled that the '… use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and the licensed indications for the medicine.' and '… the analgesic efficacy of BuTrans in such patients could not be substantiated'. The case was reported to the Appeal Board because the '... Panel was concerned that the promotional material at issue was inappropriate .... Promoting a medicine in a patient group in whom there was no robust evidence of efficacy was an extremely serious matter'.

Napp submitted that in the context of the Panel's rulings it responded to ruling 1 and the reasons for the report to the Appeal Board together because there was significant overlap between both. Napp first responded to the reasons for the report to the Appeal Board and explained why it was appropriate to promote BuTrans for pain in dementia. The promotion of BuTrans for the treatment of pain in dementia was appropriate and not misleading.

Napp submitted that all three doses of BuTrans were licensed for 'the treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia'. Pain in patients who suffered from dementia represented a patient population with chronic pain and was therefore within the licensed indication. Dementia was a co-morbidity to chronic pain rather than dementia being a specific pain syndrome.

There was no difference in the pharmacological treatment of a patient suffering from chronic non-malignant pain whether they had dementia or not. Similarly, where dementia was a co-morbidity to other medical conditions, these conditions were still managed in the same way eg for patients with osteoporosis or pneumonia, bisphosphonates were used and appropriate antibiotics whether or not they had dementia.

Napp noted that the European Medicines Agency (EMA) had set out specific recommendations for pharmaceutical companies when developing new medicines for nociceptive pain (Committee for Proprietary Medicinal Products Guidance document for treatment of nociceptive pain 2009). In these regulatory guidelines there was no requirement to conduct specific pain in dementia studies and there was no specific pain in dementia indication. Further to this, the guidance stated that results could be extrapolated to elderly patients providing appropriate pharmacokinetic studies were conducted. In this regard, Napp had shown that no dose adjustments were required for BuTrans either in the elderly or in patients with renal impairment (BuTrans SPC). Dementia patients were often elderly and consequently suffered from significant renal impairment due to the ageing process. Therefore, in this context, BuTrans was a rational and sensible option to treat pain in this population. This was in contrast to the commonly prescribed opioids especially codeine, morphine and oxycodone, which were not recommended for chronic pain management of patients with severe renal impairment (Palliative Care Formulary, Twycross 2011).

Napp submitted that dementia patients felt pain in the same way as those without dementia (Kunz *et al* 2008) and that pain was under-recognised and undertreated in dementia patients (Horgas *et al* 1998 & Reynolds *et al* 2008). Further, clinicians, were bound by the General Medical Council's (GMC's) Duties of a Doctor, which specifically stated that they should 'take all possible steps to alleviate pain and distress whether or not a cure may be possible' (Good Medical Practice (GMP) Guidance 2013). The GMC also stated that 'You must take prompt action

if you think that patient safety, dignity or comfort is or may be seriously compromised' and that 'whether or not you have vulnerable adults or children and young people as patients, you should consider their needs and welfare and offer them help if you think their rights have been abused or denied' (GMP) Guidance 2013).

Napp stated that in the context of the wider literature, there was limited evidence for the treatment of pain using various analgesics in dementia because there was no difference in the pharmacological treatment of pain in a patient with or without dementia. This was reflected upon performing a comprehensive literature search as, aside from Husebo *et al*, its associated publications (Husebo *et al* 2011, Husebo *et al* 2014 and Sandvik *et al* 2014) and some earlier work which also investigated the effect of treating pain on behavioural outcomes (reviewed in Pieper *et al* 2013), there was only one trial in 39 patients that looked at effectiveness of an analgesic medicine for pain in patients with dementia (Buffum *et al* 2004).

Napp submitted that a health professional treating chronic pain in a dementia patient was faced with a number of clinical considerations to take into account. BuTrans made a rational choice for analgesia in this difficult-to-treat patient group because it provided consistent pain relief for up to seven days (BuTrans SPC). The convenience of a transdermal preparation that required changing every 7 days reduced administration time and staffing requirements in residential and nursing homes (Barber *et al* 2009). Napp noted that treatment compliance in dementia patients was challenging (Small *et al* 2007). However, patients on BuTrans showed greater treatment persistence vs codeine and tramadol over 6 and 12 months in over 4,900 patients of which 64% were older than 65 years (Gallagher *et al* 2009). Further, BuTrans offered an alternative method of administration in patients who had either difficulty swallowing or refused to swallow and the convenience of a weekly patch could ease the daily pill burden on patients (Conaghan *et al* 2011, Karlsson *et al* 2009). Napp again stated that although dementia patients were often elderly, BuTrans did not require dose adjustment in elderly patients or in those with severe renal impairment (BuTrans SPC). BuTrans was a viable alternative to codeine or tramadol as it was licensed for moderate pain and its dose equivalence range was within the licence range of codeine and tramadol's indication for pain (BuTrans SPC, codeine SPC and tramadol SPC) and the tolerability profile of BuTrans was comparable to that of other opioid analgesics including codeine and tramadol (Karlsson and Berggren 2008 and Conaghan *et al* 2011).

Napp had asked a university professor of ageing and geriatric medicine for his expert clinical opinion on this issue. He stated that 'clinically there is a constant emphasis that a diagnosis of dementia should not deny patients the same management as that afforded to those without a diagnosis of dementia. There is a very limited evidence base for the use of analgesia in older people. Therefore it is logical to use BuTrans in a stepwise approach to manage pain in the dementia population in the same way as would be the approach in patients without dementia.'

Napp noted that the Panel's ruling included comments regarding the adverse event profile of BuTrans including stating that 'confusion' was common in these patients (BuTrans SPC). Whilst this was important to be aware of, there was no contraindication or special warning against use in dementia within the BuTrans SPC.

Napp finally noted that despite being found in breach (ruling 2), the Panel in ruling 1 did not find Napp in breach with respect to the BMJ advertisement. The advertisement depicted a difficult-to-treat dementia patient suffering from pain, the Panel stated that 'it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients'. This inferred the advertisement taken as whole, encompassing both the image and text, demonstrated a focus on pain and was not misleading with respect to the promotion of pain in dementia. Napp noted that the BuTrans pain in dementia sales-aid depicted the same patient as the advertisement in addition to further background on pain in dementia, why BuTrans 'makes sense' for managing pain in dementia and concluding 'See behavioural changes, check for pain, consider BuTrans'.

Napp submitted that with respect specifically to the pain in dementia webpage, taken as a whole encompassed only two pages (or 1.3%) of the BuTrans website totalling 150 pages, which was clearly focused on the management of pain.

In summary, Napp refuted the Panel's rulings and submitted that it was appropriate to promote BuTrans for the treatment of pain in dementia as this was within the licensed indication of the 'treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia'. There was no regulatory requirement to have specific pain in dementia data or indication. There was an ethical obligation to manage pain in patients who had dementia in the same way as managing pain in patients without dementia and clinically BuTrans made a highly rational option for the treatment of chronic pain in this difficult-to-treat patient group.

Part 2: Panel ruling 2a) Husebo

Napp noted that much of the debate centred on the Husebo study first published in the BMJ in 2011 (Husebo *et al* 2011) with post-hoc analysis published more recently (Husebo *et al* 2014 and Sandvik *et al* 2014).

Background

Napp submitted that the NICE Dementia Guidelines, (NICE CG42) the DoH (2009) Bannerjee Report on the use of antipsychotics in dementia patients and current guidelines from the Alzheimer's Society (2011) recommended that the first line management of behavioural and psychological disturbances (BPSD) in dementia should be a detailed assessment to identify any treatable causes. These included

delirium, depression and pain; such indicators for pain in a person with dementia included either withdrawn or disturbed behaviour.

Napp stated that failure to diagnose and treat causes of agitation and aggression in dementia patients had in part led to the over use of antipsychotics, which was associated with an increase in the number of cerebrovascular adverse events and deaths in dementia patients (Bannerjee 2009).

Napp submitted that a number of studies had confirmed the correlation between pain or discomfort and agitation in dementia patients (Pelletier and Landreville 2007, Ahn and Horgas 2013 and Zieber *et al* 2005). This had included a study of nursing home based dementia patients that demonstrated pain severity was positively linked to the frequency of agitated behaviours (Ahn and Horgas 2013).

Clinicians had the same ethical duty to manage pain in dementia as with patients who had pain without dementia. As previously outlined, in the GMC's GMP Guidance stated that doctors should 'take all possible steps to alleviate pain and distress whether or not a cure may be possible'.

Napp submitted that pain was both a clinical and subjective diagnosis, usually where the patient told you they were in pain. There were no clinical investigations that would confirm or refute the diagnosis. In dementia, patients were often verbally and cognitively impaired so struggled to communicate how they felt. This meant that the diagnosis of pain in a patient with dementia was more difficult to make than in a normal adult. It was often a diagnosis of exclusion (Royal College of Physicians, British Geriatrics Society and British Pain Society (RGP, BPS, BGS) Guidelines 2007) and clinicians should consider empirical analgesic trials or other pain-relieving interventions in patients who they thought were in pain might.

Context of the study

Napp submitted that based on the previous points the Husebo study was therefore a pragmatic investigation which recognised the established link between pain and agitation in patients with dementia and that behavioural disturbances played a critical role in the identification and management of pain in dementia. This pragmatic approach was fully in line with professional guidelines such as the RCP/BPS/BGS Guidelines which recognised that patients with dementia who were in pain might not complain of pain directly but might exhibit behavioural disturbances. Consequently Napp submitted that the Husebo study was conducted within the licensed indication for BuTrans.

Napp submitted that it clearly intended to demonstrate the impact that under-recognised pain had in dementia patients which was consistent with guidelines including the NICE dementia guidelines (NICE CG42), the DoH Bannerjee report and the Alzheimer's Society guidance 2011).

Napp submitted that with respect to Husebo *et al* (2011), it had clearly stated in both the webpage and sales aid that a step-wise approach to pain management was carried out (using various analgesics) and that BuTrans, which was licensed for moderate chronic pain, was a part of this approach. Napp did not claim that BuTrans directly improved agitation and aggression in dementia, nor did it claim that BuTrans alone was responsible for the observed finding. Therefore, Napp submitted that as suggested in the original complaint, the wording was indeed carefully chosen to reflect in the first instance that a step-wise approach to pain management was used, whilst secondly reflecting that BuTrans was part of (ie 'was associated with') the step-wise approach to the management of pain. However, Napp duly acknowledged that it could have explained Husebo *et al* (2011) in more detail surrounding those patients who were treated with BuTrans.

Beyond Husebo

Napp finally noted that Husebo *et al* (2011), referenced on the pain in dementia webpage, was only one of thirteen references which supported both the clinical background to pain in dementia and the rational use of BuTrans in the treatment of chronic non-cancer pain in this specific population. Many of these papers had already been cited in this response. This included the BuTrans SPC with licence information for clinicians and a Napp study which demonstrated BuTrans provided 7 day consistent efficacy (BuTrans SPC and Napp data on file BP98-0201). In addition Gallagher *et al* (2009) demonstrated patients on BuTrans showed greater treatment persistence vs codeine and tramadol. There were also four observational studies which demonstrated a high prevalence of pain in dementia patients in nursing homes (Zwakhalen *et al* 2009) and they returned similar pain scores as non-cognitively impaired patients (Closs *et al* 2004) but were prescribed less analgesics (Closs *et al* 2004 and Horgas and Tsai 1998). Further, there were three reviews on the under-treatment of pain in dementia (Cook *et al* 1999), the management of chronic pain in the elderly using transdermal buprenorphine including BuTrans (Vadivelu and Hines 2008) and a general review of BuTrans for treatment of pain (Plosker 2011). Finally, there was a DoH report on the overuse of antipsychotics in dementia (Bannerjee 2009) and an example of a local UK factsheet on pain in dementia (Sampson and Kitchen 2005).

In summary, Napp submitted that the Husebo study was a pragmatic investigation which recognised that behavioural disturbances played an important role in the identification and management of pain in dementia. The claims and substantiation for the use of BuTrans should also take into account the total literature base and not simply Husebo. Finally, for the reasons outlined previously the promotion of BuTrans for the treatment of pain in dementia was appropriate even without the Husebo study.

In the context of the above response, Napp therefore disagreed there had been a breach of Clauses 7.2 or 7.4.

Part 2: Panel ruling 2b)

'There was no evidence that treatment with BuTrans limited the unnecessary use of antipsychotics' and '... the statement was misleading by implication and could not be substantiated.'

Napp submitted that in its response it had outlined why it had not made a claim on antipsychotic usage and these key points still stood. In the context of the pain in dementia website Napp had not stated that BuTrans was associated with reduced antipsychotic usage, BuTrans was not mentioned in the sentence in order to distinguish it from the claim.

Napp submitted that to further substantiate this position, it was an established important clinical problem that antipsychotics were overused to treat behavioural and psychological disturbances (BPSD) in dementia including agitation and aggression. This overuse of antipsychotics was estimated to cause more than 1,620 cerebrovascular adverse events and more than 1,800 deaths per year (Bannerjee 2009). Napp submitted that it was therefore recommended that the first line management of BPSD should be a detailed assessment to identify any treatable causes, which included pain, before antipsychotics were even considered (Bannerjee 2009, NICE CG42, Alzheimer's Society Guidelines 2011). In this context Napp submitted that its intention was to raise awareness that 'effective management of pain can play an important part in the treatment of agitation and could reduce the number of unnecessary prescriptions for psychotropic drugs in this population' (Husebo *et al* 2011). Napp submitted that it had been careful not to mention BuTrans in the statement above, however it understood that there could be a perception by association but that was certainly not its intent.

Napp submitted that in the context of the above clinical guidance, it therefore did not agree there had been a breach of Clause 7.2 or 7.4.

Napp submitted that taking into consideration the reasons presented it considered that it was rational and clinically appropriate to promote BuTrans for the treatment of moderate chronic pain in dementia patients. As there was no difference in the pain pathophysiology there was no regulatory requirement to conduct specific clinical trials in this dementia patient population. Therefore, Napp did not agree that it had been misleading with regard to the evidence base and the licensed indication for BuTrans in the treatment of non-malignant pain of moderate intensity. In addition, Napp had also addressed the ruling with regards to claims for the analgesic efficacy of BuTrans in dementia patients. Napp included the Husebo paper as it was an important study which highlighted that proper step-wise pain management in this difficult to assess population could improve agitation and aggression. Napp contended that BuTrans was a sensible clinical choice for the treatment of moderate chronic pain in dementia patients not solely based upon the Husebo data but also by considering all of the literature quoted on the BuTrans pain in dementia webpage (thirteen references), within the advertisement (five references) and the sales aid (thirty references).

To conclude, Napp submitted that it took compliance very seriously and it felt strongly that the BuTrans pain in dementia campaign was appropriate given its response.

COMMENTS FROM THE COMPLAINANT

Antipsychotic reduction – the sales aid

The complainant noted that Napp had submitted that the webpage statement about antipsychotic use was a general statement which focussed on the potential reduction in the amount of antipsychotic prescriptions if pain was properly managed and that BuTrans itself was not claimed to cause reduction of antipsychotic use. The relevant text from the sales aid was:

> 'That's why once-weekly BuTrans patches are a sensible choice in dementia:
>
> - Can help improve pain-related behavioural changes as part of a pain management program, limiting unnecessary use of antipsychotics.'

The complainant alleged that the use of the word 'can' rather than 'may' meant that this went beyond a 'general statement' and suggested at least a subgroup (ie those with pain-related behavioural change) in whom antipsychotic use was limited.

Referencing

The complainant noted that Husebo *et al* (2011) was used as reference 11 to support the following four assertions:

1 'The limited ability of dementia patients to communicate effectively often leads to inappropriate use of antipsychotics before factors such as pain are explored[10,11]'.

The complainant had been unable to find this assertion anywhere in either reference. Reference 10 was to a comprehensive 62 page report on antipsychotic prescribing in dementia for the DoH (Bannerjee 2009). The only reference to pain in the report was as follows:

> 'The first line of management should be detailed assessment to identify any treatable cause of the BPSD (eg delirium, pain, depression); this should include taking the history of the problem, having the behaviour described by the carer/team, discussing current and past behaviour with the carer/team.'

2 'Effective management of pain can play an important part in the treatment of agitation and could reduce the number of unnecessary prescriptions for psychotropic drugs in this population[11]'.

The complainant alleged that this was actually a misquotation of the original which read: '... effective treatment approach for people with dementia and agitation, improved management of pain should also help to reduce the number of prescriptions for

anti**psychotics** in this population' (emphasis added by the complainant). The fact that the authors chose to dilute the message from the discussion of the academic paper suggested that they were entirely aware of the potential impact of claims concerning antipsychotic reduction.

3 'Effectively managing pain in dementia **can** help reduce behavioural disturbances limiting the unnecessary use of antipsychotics [10,11]' (emphasis added).

The complainant alleged that the 'can' here was stronger than statements in either reference. Husebo *et al* (2011) stated: 'The results also highlight the **potential** value of effective treatment of pain as a key part of reducing the use of antipsychotics and other psychotropic drugs in residents of nursing homes' and (as above) '... effective treatment approach for people with dementia and agitation, improved management of pain **sh**ould also help to reduce the number of prescriptions for antipsychotics in this population' (emphasis added).

4 'A step-wise approach to pain management, which included BuTrans was associated with reduced agitation, neuropsychiatric symptoms and pain compared with those receiving their usual treatment and care [11,12]'.

The complainant alleged that this was due to paracetamol not ***BuTrans***.

The complainant noted that reference 12 (Plosker 2011), was a comprehensive 18 page review about transdermal buprenorphine for pain. It was written by a staff author on the Adis review journal 'Drugs'. The single reference to 'dementia' in this 18 page review simply reprised the Husebo study as follows:

> 'Also noteworthy are results of a further randomized controlled trial, which suggest that transdermal buprenorphine, as part of a stepwise systematic approach to pain management in patients with concurrent dementia and chronic non-malignant pain, was associated with reduced agitation and overall neuropsychiatric symptoms, as well as improved pain relief, when compared with a control group receiving usual treatment and care.'

The complainant noted that this 'doubling up' in the referencing for this assertion in the sales aid (point 4 directly above), and also in Napp's response, was therefore misleading as it implied that a greater weight of evidence existed than was actually the case.

The complainant noted that reference 12 was also quoted in the sales aid as follows:

- 'BuTrans has a similar tolerability profile to that of other opioid analgesics[12].'

The relevant extracts from the section of the review on tolerability stated:

> 'In active-comparator clinical trials discussed in section 4, transdermal buprenorphine had a broadly similar tolerability profile to that of orally administered co-codamol[34] and prolonged release tramadol,[32] but was better tolerated than sublingually administered buprenorphine;[31] observed differences in the local tolerability profile reflect the different routes of administration. The most frequently reported adverse events with transdermal buprenorphine plus oral paracetamol versus oral co-codamol in patients with osteoarthritis were as follows: nausea (40% vs 25%), erythema at application site (27% vs 0%), constipation (26% vs 32%), pruritus at application site (17% vs 0%), dizziness (14% vs 6%) and vomiting (11% vs 8%).[34] In the comparative trial with tramadol, 14.5% of patients treated with buprenorphine and 29.2% of tramadol recipients withdrew from the study because of adverse events.[32]
>
> ... (with reference to placebo controlled trials) ....
>
> In a study in patients with osteoarthritis pain, 16.9% of all reported adverse events with transdermal buprenorphine 5–20 µg/h were deemed to be severe; the corresponding figure in the placebo group was 9.9%.[30] The most frequently reported adverse events with transdermal buprenorphine (n = 100) and placebo (n = 99) in the ITT population were gastrointestinal disorders (57% vs 25%), application site reactions (61% vs 40%) and CNS disorders (45% vs 18%). These were also the most common categories of adverse events in randomized, double-blind, placebo-controlled trials with transdermal buprenorphine in patients with chronic back pain,[36,37] and in a 6-month openlabel extension. [36].
> ...
>
> Older patients (≥65 years) had a higher incidence of constipation, dry mouth, diarrhoea, dizziness, fatigue and somnolence than patients aged <65 years, whereas headaches and application site reactions were reported more frequently in the younger cohort [52]'.

The complainant noted that reference 52 was to an abstract (Wen, Lynch, Munera *et al*, J Pain 2011) and he could not find further data on this point.

The complainant noted that the EMA note for guiding clinical investigation of medicinal products for treatment of nociceptive pain stated: '**As a rule** the results obtained in the general trial population can be extrapolated to the elderly patients provided appropriate pharmacokinetic studies are conducted' (emphasis added by the complainant). The Wen abstract suggested that, whatever the pharmacokinetic results indicated the elderly might break this rule.

A 'sensible choice'?

The complainant noted that in the sales aid, references 22-24 were used to support the assertion that:

> 'Butrans is a sensible choice ... that suits the challenges of dementia.[22-24].'

The complainant noted that reference 22, Priano *et al* (2006) was a wide ranging review of transdermal treatment of neurological disorders in the elderly. The complainant was unable to get a copy, but the advantages of patches was uncontentious.

The complainant noted that reference 24, Rinaldi *et al* (2005) reported an observational study of 419 outpatients with dementia (Mean Mini Mental State Examination (MMSE) =13). It reported that carer burden, distress, depression and anxiety were related to higher scores on behavioural disturbance and agitation in the patient. It did not refer to pain or any analysis relating to medication of any type. Whilst the complainant accepted that this pointed to a challenge of agitation in dementia, he/she alleged that it did not really support the idea that BuTrans was a sensible choice.

The complainant noted that reference 23, Manfredi *et al* (2003) seemed to be used to support the idea that opiates might have a role in managing agitation. The study was directed at agitation rather than pain. It did not use BuTrans. It found no effect on agitation of opiates. In this blinded, non-randomised, study patients were excluded if they were either sufficiently cognitively intact to be able to report pain reliably or if they had an 'obviously painful condition' which required active management. Despite these pain-related exclusion criteria, the median number of painful conditions was 5 (range 0-10). Mean MMSE=6. Inclusion criteria included persistent agitation for at least 3 months despite 2 psychotropics. Patients were all given 4 weeks of placebo then 4 weeks of an opioid (long acting oxycodone or, for those unable to swallow pills, long acting morphine). Of the 25 cases who completed 4 weeks of opiate, there was no difference in the primary outcome (agitation score) at the end. A further 11 cases dropped out in the placebo phase and 11 in the opiate phase. A *post hoc* analysis of 13 patients over the age of 85 years suggested that physical agitation was reduced.

The complainant thus alleged that references 23 and 24 did not support the claim that BuTrans was a 'sensible choice that suits the challenges in dementia'. Reference 23 was irrelevant and reference 24 did not have a sound statistical basis. To cite them in this way was misleading.

Clinical data cited in Napp's response

The complainant noted that in its appeal, Napp had referred to Buffum *et al* (2004) as the only other trial of pain relief in dementia. This double-blind, placebo controlled, crossover study of 39 patients with severe dementia who were not already on pain medication, showed that 650mg four times a day paracetamol had no effect on pain scores. The authors suggested that the results showed that paracetamol was 'inadequate for ... patients ... with significant discomfort'. However, the complainant alleged that there were two other possible explanations. Firstly, it was also possible that what was being measured was, in fact, agitation which had nothing to do with pain: in other words, analgesia was the wrong approach. There was a tautology linking pain or discomfort with agitation in dementia: the items assessed by scales used to measure 'discomfort' (such as the PAIN-AD, and its predecessor the DS-DAT which was used here) overlapped very substantially with scales used to measure 'agitation'. Secondly, it was also possible that staff in the care homes were good at distinguishing patients with genuine pain from those with agitation and had already started analgesia. 'Already on analgesia' was the reason for exclusion of 22% of potential participants.

With regard to the slides referred to by Napp the complainant noted that:

- Ahn and Horgas (2013) showed, in analysis of the minimum dataset (MDS2.0) scores of nursing home residents with dementia (N=56,577), a 4% increase in risk of aggression in patients with pain (95%CI OR=1.01-1.08) and a 17% increase in agitation (95CI OR=1.13-1.20).

- Pelletier and Landreville (2007) found no relationship between 'aggressive behaviour' and discomfort in 49 nursing home residents. In contrast, discomfort accounted for 30% of the variance in 'verbally agitated behaviour' which comprised 'complaining, constant requests for attention, negativism, repetitious sentences or questions, screaming.

- Vadivelu and Hines (2008) (cited in the BMJ advertisement) reviewed transdermal buprenorphine in the elderly and the only (unreferenced) mention of dementia was 'transdermal buprenorphine will be a useful tool for the administration of drugs (sic) when patients are forgetful, or are unable to swallow oral medications'.

- Pieper (2013) (cited in the BMJ advertisement) was a systematic review of either a) interventions targeting pain with or without behavioural disturbance, or b) pain interventions targeting behaviour.

Pharmacological studies

The complainant noted that the 6 included studies of the pharmacological treatment of pain in dementia included Husebo *et al* (2011), Buffum *et al* (2004) and Manfredi *et al* (2003) (discussed above). Passmore (2011) was a case report of successful treatment of a 104 year old man with sublingual sufentanil. Elliott (2009) reported an ABAB (no intervention baseline (A1), and intervention phase (B1), with each phase repeated (A2 and B2)) withdrawal of paracetamol from 3 patients which showed reduced guarding, grimacing and vocalisations when on paracetamol. In Chibnall (2005) 25 patients were randomly assigned to paracetamol or placebo. The complainant noted that there was no effect on agitation.

Complex interventions

The complainant alleged that of the 9 included studies identified as targeting 'both pain and behaviour' in dementia, only 2 were relevant because they allowed inclusion of analgesia

interventions. Kovach (2006) was rated as the best quality randomised controlled trial. This was a trial in 114 people of a complex intervention of 4 weeks of stepped care. It showed benefit on 'discomfort' but not on behaviour. Analgesia, which was step 4 of 5, was prescribed to 26 of 57 in the interventions arm. Whilst it was effective in 15/20 cases, the prescription was for a 'narcotic' in only 5 cases. No further details were available. Chapman and Toseland (2007) was a 2x2 partial cross over trial of advanced illness care teams which was effective in reducing pain and agitated behaviour. This was published in the Journal Social Work and the complainant had not been able to get a copy.

In summary, the complainant alleged that the best evidence was that pain in dementia increased the odds of aggression by 4%. There was no evidence that opiates were of any benefit in dementia.

The complainant alleged that the citations in the promotional material were misleading because they implied that there was an evidence base to support the clinical approach of: 'See behavioural changes, check for pain, consider BuTrans in dementia'.

Ethical and GMC obligations

The complainant noted Napp's contention that the ethical obligation for the clinician here was clear. One should treat pain where one saw it. Pain was certainly worth considering when faced with an agitated patient with dementia.

The complainant noted that there were no trials registered for buprenorphine and dementia on Clinicaltrials.gov or the International Standard Randomised Controlled Trial Number register, suggesting that Napp had no imminent plans to improve the quality of the evidence base to support the marketing of its product for this population.

In summary, the complainant noted that conducting trials in patients with dementia was difficult, and trials in dementia patients with agitation were amongst the most challenging in medicine. Husebo and her colleagues had done a good job in advancing this field but had not produced evidence of any benefit for BuTrans. It was unfortunate therefore that this trial appeared to have been the main stimulus for Napp's promotional campaign.

The complainant stated that patients with dementia – some of whom complained, were negative and constantly requested attention – had been subjected to over-prescription of almost all classes of psychoactive medication: benzodiazepines then antipsychotics. When it was not only asserted that agitation was a sign of pain which could not be otherwise expressed, but also pain scales included items which were agitated behaviours, then clinicians were likely to be drawn into an irrefutable tautology. When combined with powerfully emotive promotion of a treatment for the agitation/pain, this was a sure route to over-treatment.

The complainant alleged that in the context of the current evidence, this promotional campaign unduly emphasised dementia as a population for treatment with BuTrans, was ambiguous as to whether it promoted BuTrans for pain or agitation, misled in its implication that BuTrans 'could' reduce antipsychotic prescribing, did not present or refer to sufficient material to allow recipients to form an opinion of its value, and used references to studies in ways which were misleading and did not have a sound statistical basis.

APPEAL BOARD RULING

The Appeal Board accepted that correctly diagnosing pain in dementia patients posed particular problems for the prescriber, the patient and their carers. Dementia patients were a vulnerable group.

The Appeal Board considered that the over-riding message of the material at issue, which included the claim 'BuTrans makes sense in dementia', was that pain was a major cause of agitation in dementia patients who could not otherwise express their pain and so a sensible choice was to prescribe BuTrans to treat such pain. The material at issue had oversimplified the treatment pathway for pain in dementia. The World Health Organisation (WHO) pain relief ladder referred to the stepwise treatment of pain. The Appeal Board noted that the website and detail aid had each referred to a '… step-wise approach …', however not until the last bullet on page 1 of the website and on page five of the detail aid. In the Appeal Board's view, the material at issue should have referred to the various steps in a stepwise treatment plan at the outset, including alternative treatments and precautions that needed to be considered before a prescriber could responsibly prescribe BuTrans for pain in dementia patients. In that regard the Appeal Board queried whether sufficient emphasis had been given to the side-effect profile of BuTrans, which included, *inter alia*, confusion as common, agitation and anxiety as uncommon and psychotic disorder as rare especially as dementia patients would be unlikely to be able to report, and prescribers and carers would be unlikely to recognise, such side effects which might appear to be part of the patient's underlying symptoms of dementia.

The Appeal Board noted that the only clinical data concerning the use of BuTrans in the treatment of pain in dementia was Husebo *et al* (2011). The primary outcome measure was agitation as assessed by a nurses' rating questionnaire. Assessment of pain using the observational MOBID-2 pain scale was a secondary outcome measure. A further analysis of the study results published after the material at issue had been approved showed that the treatment effect of BuTrans was not apparent until week eight of the eight week study. The 39 BuTrans patients in the study had not been positively diagnosed with non-malignant pain of moderate intensity such that they required an opioid, nor was it clear that they did not have acute pain. The Appeal Board noted the Panel's concerns about the study and Napp's response to these points in its appeal. The Appeal Board noted from the Napp representatives at the appeal that Husebo *et al* (2011) was not powered to measure the effect of BuTrans on pain in patients

with dementia. The Appeal Board considered that Husebo *et al* (2011) was not sufficiently robust to support the claims about the use of BuTrans in the treatment of pain in patients with dementia.

The Appeal Board thus considered that the material at issue which promoted the use of BuTrans to treat pain in dementia was misleading with regard to the evidence base and claims for analgesic efficacy in such patients could not be substantiated. The Appeal Board noted that treating dementia patients in pain with BuTrans was not inconsistent with its licensed indication as long as those patients had non-malignant pain of moderate intensity such that an opioid was necessary for obtaining adequate analgesia. However, to have a campaign which actively promoted its use based on data in a sub-group for whom there was no robust analgesic evidence was of concern. The Appeal Board was particularly concerned about the safety of using BuTrans in this vulnerable patient group given that if they did not have the verbal skills to express and communicate pain then they were also unlikely to be able to express and communicate side-effects such as confusion and anxiety etc. The Appeal Board thus upheld the Panel's ruling of a breach of Clauses 7.2 and 7.4. Napp's appeal on this point was unsuccessful.

The Appeal Board noted that the claim on the website 'Effectively managing pain in dementia can help reduce pain-related behavioural disturbances, limiting unnecessary use of antipsychotics.' appeared below the heading 'BuTrans makes sense in dementia'. A similar claim appeared on pages five and eight of the detail aid which was headed 'BuTrans is a sensible choice …'. The Appeal Board considered that in the context in which they appeared, these claims could only be referring to the effect of BuTrans. The Appeal Board considered that Napp had not provided evidence to show that the use of BuTrans limited unnecessary use of antipsychotics. The Appeal Board thus upheld the Panel's ruling of a breach of Clauses 7.2 and 7.4. Napp's appeal on this point was unsuccessful.

With regard to the advertisement, the Appeal Board considered that given the strap line 'Dementia hurts enough without pain' it was sufficiently clear that the advertisement promoted BuTrans for pain relief in dementia patients and not for the treatment of agitation. On this narrow allegation the Appeal Board upheld the Panel's ruling of no breach of Clause 7.2. The complainant's appeal on this point was unsuccessful.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted its concerns and rulings above and that the Panel had required the material to be suspended pending the final outcome of the case. Given its rulings of breaches, the Appeal Board noted that the material at issue would now have to be withdrawn. The Appeal Board decided, in this instance, to take no further action in relation to the report from the Panel.

Complaint received **23 July 2014**

Case completed **7 November 2014**