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# Treatment with the direct oral anticoagulants (DOACs) apixaban and rivaroxaban associated with significant worsening of behavioural and psychological symptoms of dementia (BPSD)

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Accepted 13 January 2021



**To cite:** Porter KMF, Hargreaves IP, De Souza S, *et al*. *BMJ Case Rep* 2021;**14**:e240059. doi:10.1136/bcr-2020-240059

## SUMMARY

We report the cases of two patients who developed worsening behavioural and psychological symptoms of dementia (BPSD), coinciding with starting the factor Xa inhibitor direct oral anticoagulant medications apixaban and rivaroxaban, respectively. Both patients required detaining under the Mental Health Act. Their symptoms improved significantly, within 2 weeks, on switching to alternative anticoagulant therapies and they were both discharged from the acute psychiatric ward. Front-line staff should partake in postmarketing surveillance of medications, completing the Medicines and Healthcare products Regulatory Agency yellow cards for example (UK). There is increasing evidence for an aetiological role of cerebral mitochondrial dysfunction in neuropsychiatric disorders. Development of a rating scale of drugs that are potentially less toxic to cerebral mitochondria could inform national prescribing guidelines and enable safer treatments to be offered to older people, reducing the likely hood of them experiencing apparent BPSD.

## BACKGROUND

Globally, the estimated proportion of the general population aged 60 and over with dementia is between 5% and 8% equating to around 50 million people. There are nearly 10 million new cases every year.[1] Ischaemic heart disease and stroke are the biggest cause of death worldwide.[2] Factor Xa inhibitor direct oral anticoagulants (DOACs) have become widely prescribed over recent years in the UK, being included as drugs recommended by the National Institute for Health and Care Excellence as achieving anticoagulation in prevention of systemic emboli in patients in atrial fibrillation (AF) or with deep vein thrombosis. A significant proportion of the population with mild cognitive impairment or dementia are, therefore, also treated with DOAC's for these coexistent diagnoses. In our experience locally, reflecting changing practice throughout the developed world, many patients are being switched from warfarin to factor Xa inhibitor DOACs, which do not require close monitoring of blood levels. Despite no listed neuropsychiatric side effects in the British National Formulary (BNF) for these, we suspected that these two patients were experiencing iatrogenic worsening of their behavioural and psychological symptoms of dementia (BPSD). We hypothesise that similar factor Xa inhibitor side effects are experienced by many older people to a varying degree and wrongly attributed to BPSD.

## CASE PRESENTATION 1

A woman in her early 80s was admitted to her local District General Hospital (DGH) following a fall. She was found to have a pulmonary embolus (PE) and to be in AF. She was commenced on apixaban. During this admission, staff raised concerns about her memory and on discharge, referred her to the local memory assessment service (MAS). Following initial MAS assessment approximately 3 weeks later, the patient was commenced on the antidepressant mirtazapine for low mood and poor sleep. However, after a further 3 weeks, she was brought to the liaison department at the DGH following physically assaulting police officers and paramedics. Her husband confirmed a deterioration in his wife's memory over 6 months with her becoming repetitive in conversation and forgetting who some of the neighbours were. She had also started to accuse him of having an affair and steeling her money over these months. He denied this saying that they spent nearly all their time together. However, he indicated that there had been a noticeable worsening of her presentation following her hospital admission 6 weeks before with a PE, with her becoming physically aggressive since, assaulting him on multiple occasions and calling the police frequently. He explained that he had had to lock himself in the bathroom that day for his own safety. At interview, the patient reported low mood and poor sleep since the alleged affair, saying that she had seen this person and found a slip in her husband's pocket. Her mood was labile, alternating between irritability and tearfulness. She was noted to be repetitive in conversation with poor recall of recent events. Her insight was poor although she was aware of recent memory difficulties. She was assessed and admitted under section 2 of the

Mental Health Act (MHA) with a provisional diagnosis of delusional jealousy in the context of likely dementia.

## INVESTIGATIONS

Physical examination was unremarkable. Medications included apixaban (5 mg two times per day), bisoprolol (2.5 mg two times per day), digoxin (125 $\mu$g one time per day) and glyceryl trinitrate spray as required. A dementia blood screen was normal. An MRI head scan showed minor generalised cerebral atrophy with a few foci within the supratentorial white matter reported as likely age related ischaemic phenomena. The patient scored 70/100 on the Addenbrooke's cognitive examination, losing marks in the memory domain and suggestive of at least mild dementia.

## MANAGEMENT

Mirtazapine was stopped as the patient's agitation and aggression had only worsened. Subsequent trials of medication to manage this included intramuscular lorazepam (0.5–1.0 mg), required on several occasions; quetiapine (125 mg daily) combined with citalopram (20 mg daily), both subsequently stopped as not effective; replaced by aripiprazole (15 mg daily), also ineffective and replaced by oral zuclopenthixol, (increased to 18 mg daily). After 2 weeks on this dose of zuclopenthixol and nearly 4 months on the acute psychiatric ward, although the patient was no longer expressing delusion ideas regarding, her husband having an affair her presentation had, if anything, worsened with regard to her agitation and aggression, throwing a chair, banging on the doors, hitting out at staff and asking for her mother. The decision was made to switch apixaban to dabigatran as an alternative DOAC. The rationale was that there had been no other obvious precipitating factors that might explain the relatively sudden and persistent deterioration in the patient's mental state and the temporal relationship with starting apixaban. She became markedly more settled over the next 2 weeks, no longer banging on doors or wanting to leave. She acknowledged feeling more calm and relaxed. There were no longer concerns regarding her mood or sleep. This was in the absence of any other behavioural approach, medication or management changes.

## OUTCOME AND FOLLOW-UP

The patient was discharged to a local care home, which would not have been considered possible prior to her switching anticoagulant medication and appearing far less agitated and aggressive. She was significantly more settled and her presentation was of mild dementia. Treatment with antipsychotic medication had been effective for her delusional beliefs throughout her admission and she continued treatment with clopixol (18 mg daily). The management plan was to reduce this while monitoring her mental state for any re-emergence of BPSD agitation and aggression. After a month, both she and her husband were enquiring about the possibility of her returning home.

## CASE PRESENTATION 2

The second case is of a man in his early 70s, described by his family as having some mild memory problems and confusion at times although managing his activities of daily living well enough. He did not think it severe enough to bother his general practitioner (GP). However, approximately a month after commencing rivaroxaban for AF, he became agitated and more confused. So much so that not only did he present to his GP, who referred him to our MAS, he was in turn referred to our older persons community mental health team, as his apparent BPSD had worsened rapidly. He had become physically threatening and aggressive towards his wife and daughters. He was assessed and admitted under the MHA and received a working diagnosis of advanced dementia. This led to trials of treatment with a variety of psychotropic medications. His apparent BPSD appeared to be treatment resistant and his presentation worsened.

At the time, in 2016, there were no side effects listed for rivaroxaban in the BNF which might have suggested the potential for worsening of mental state or cognition. However, in the absence of any other identifiable psychosocial or pathophysiological causes or changes to medication, we switched rivaroxaban to warfarin. We saw a significant improvement in the patient's presentation within 2 weeks. Importantly, further improvements were noted on gradually reducing and discontinuing the psychotropic medications that were being prescribed in an attempt to manage his change in behaviour. This patient had also became settled sufficiently to be discharged. He caught the bus home, a fact he was able to recount to us in clinic a month later when his clinical presentation was also of mild dementia.

## DISCUSSION

Front-line healthcare staff in acute settings and the community manage a heavy workload. It is all too easy to overlook potential neuropsychiatric drug side effects, especially if they are not clearly listed. They may be easily missed among older patients and wrongly attributed to dementia.

Rivaroxaban is structurally related to the antibiotic linezolid, which has been reported to cause mitochondrial toxicity.[3] Premarketing in vitro studies concluded the risk of mitochondrial toxicity associated with this anticoagulant to be low.[4] However, a more recent in vitro study, using rat kidney mitochondria, reported evidence of mitochondrial swelling and a collapse of the membrane potential following exposure to low doses of rivaroxaban.[5] The effect of apixaban, which is structurally related to rivaroxaban, has yet to be investigated on mitochondrial function.[6]

Recent research supports not only an association between reduced cerebral mitochondrial function and neuropsychiatric symptoms and disorders, but also the aetiological role it may play.[7]

There is a need for a far greater awareness and understanding of the potential cerebral mitochondrial toxicity of drugs commonly prescribed to our older populations. These are numerous and include, for example, some of the drugs prescribed for diabetes (metformin) and raised cholesterol (statins) as well as many of those prescribed for neuropsychiatric symptoms such as trazadone and sodium valproate.[8]

Asthenia (abnormal physical weakness or lack of energy) has more recently become listed as a common/very common side effect of rivaroxaban in the BNF. This is presumably as a result of the medicines and healthcare products regulatory agency (MHRA) yellow card reporting of suspected adverse reactions being submitted. This clinical symptom may be associated with mitochondrial toxicity.[9] Interestingly, Karlsvik *et al* reported no increase in the level of fatigue after initiation of treatment with rivaroxaban.[10]

Further research could enable the compiling of a cerebral mitochondrial toxicity burden scale of drugs, similar to that

as already exists for anticholinergic burden on cognitive functioning.[11] There are research techniques that can assess cerebral mitochondrial dysfunction using non-invasive brain scanning of lactate levels, which are considered to be a good correlate of mitochondrial function.[12] Such a scale could inform clinical decision making, switching patients to drugs that are potentially less toxic to cerebral mitochondria, when appropriate.

We may then be able to significantly improve quality of life and reduce the burden and cost for patients, their carers, psychiatric services and the social care system by potentially avoiding psychiatric admission and placement in dementia care homes with fees, in the UK of between £34 000 (residential) and £47 000 (nursing) per annum.[13]

## Patient's perspective

Something changed when I was in hospital after my fall, something wasn't right. I feel calmer and much better now, ready to go back home with my husband.

## Learning points

- Consider drug-induced neuropsychiatric symptoms in older patients with suspected behavioural and psychological symptoms of dementia (BPSD). Avoid assuming that their worsening presentation is necessarily secondary to cerebral emboli because they have a degree of vascular pathology on brain imaging and are in atrial fibrillation.
- Older patients are particularly prone to experiencing neuropsychiatric side effects of drugs that may not have been apparent during preclinical trials. Polypharmacy and associated drug interactions are also more common. All front-line staff should be encouraged to discuss with colleagues any medicine safety concerns, which can be particularly hard to unpick from BPSD, and to report these via the medicines and healthcare products regulatory agency yellow card system, for example.
- Neuropsychiatric symptoms and disorders are known to be associated with reduced cerebral mitochondrial function. There is an increasing body of research supporting that this relationship is aetiological. If so, any further drug-induced impairment of cerebral mitochondrial function could, therefore, be expected to precipitate or exacerbate such symptoms or disorders already present potentially.
- An increased awareness of which drugs are less toxic to cerebral mitochondria, with the development of a rating scale for example, could inform prescribing guidelines (National Institute for Health and Care Excellence) and safer treatments being offered to older people, reducing the likely hood of them experiencing apparent BPSD and requiring psychiatric detention.

**Contributors** IPH, KMFP, SDS and RG conceived the case review article. KMFP, SDS and RG where directly involved in the clinical management of the two cases cited. IPH shared his expert knowledge of the potential mitochondrial toxicity of drugs. KMFP carried out the literature search. RG and KMFP drafted the first manuscript. All authors contributed to revising and approving the final manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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