How do we define valvular heart disease when considering warfarin or dabigatran in patients with atrial fibrillation?

Dear Editor,

I have a query from the summary article "An update on antithrombotic medications: What does primary care need to know?", BPJ 73 (Feb, 2016) that I would very much appreciate some further information on.

The article makes this comment:

> *"**Dabigatran should NOT be prescribed to patients with valvular heart disease:** patients with mechanical heart valves who take dabigatran are at an increased risk of bleeding or experiencing a thromboembolic event compared to what their risk would have been if they had been prescribed warfarin."*

I understand that dabigatran is only indicated for non-valvular AF [atrial fibrillation] and is contraindicated in the presence of mechanical heart valves. What is the definition of "valvular AF" in this context? This comment seems to imply that it is the presence of a mechanical heart valve that defines the patient as having valvular heart disease. However this is clearly not the case.

Can dabigatran be used in patients with AF who have tissue prosthetic valves? Can it be used in patients with defective valves which have had a valvuloplasty but not a replacement? Can it be used in patients who have leaky or stenotic valves but have not had operative management – and if yes, at what degree of severity does it become contraindicated?

I have heard a cardiologist at a CME event say that it is contraindicated in patients whose AF is due to valvular heart disease, however it was never explained how one could be sure that the AF was due to the valve dysfunction rather than some other cause.

Further clarification about this issue would be very much appreciated.

Dr Andrew Reid, General Practitioner
Tuakau

The bpac^{nz} editorial team asked cardiologist Stewart Mann to respond:

This is a very relevant question and one that probably does not yet have a definitive answer. The RE-LY trial that compared the efficacy of warfarin and dabigatran had the exclusion criterion "moderate or severe mitral stenosis". This study also excluded patients with a potentially reversible cause of AF which might include some valve disease amenable to surgery. Other valve disease could be included. An analysis of patients with valve disease included in the trial has been conducted and published in abstract form.[1] In the RE-LY trial, around 20% of patients had valve disease, most with mitral regurgitation but some with aortic regurgitation, aortic stenosis or mild mitral stenosis. There is no mention of patients with tissue valve prostheses or of those who might have had a valvuloplasty. The group with valve disease had poorer outcomes than those without valve disease but there was no significant difference between those on warfarin or those taking dabigatran.

I would be personally wary of using dabigatran in patients with rheumatic mitral stenosis of any severity (including those who have undergone mitral valvuloplasty) but in the absence of this, dabigatran would appear to have no particular disadvantages compared with warfarin in patients with valve disease.

Of course the outcomes for those with mechanical prosthetic valves have been clearly worse with non-vitamin K antagonists such as dabigatran and so much so that I cannot even see a further trial being done in this group who are therefore left with no option other than warfarin.

Associate Professor Stewart Mann
Department of Medicine
University of Otago, Wellington

References

1. Ezekowitz MD, Parise H, Nagarakanti R, et al. Comparison of dabigatran versus warfarin in patients with atrial fibrillation and valvular heart disease: The RE-LY trial. J Am Coll Cardiol 2014;63:A325. doi:10.1016/S0735-1097(14)60325-9

Medical cannabis: an oxymoron or is there evidence of benefit?

Dear Editor,

I think most of us have a fair idea of the value of "medical tobacco" and even a reasonable idea about "medical alcohol". I am aware that "medical cannabis" is great for reducing motivation, increasing motor vehicle accidents, sedating or obtunding, and truly does help nausea while occasionally giving intractable vomiting, plus enhancing psychotic conversion rates.

Looking around, I note that Web MD suggests usage in that classic "triad" of leprosy, piles, dandruff and obesity. Not sure what it does for intelligence, but the term "dope" probably gives some insight. I note "medical cannabis" has not found much mention for mental health. Please advise. With thanks and keep up the superb work.

Dr Roger Deacon, General Practitioner
Invercargill

Response from bpac^{nz} editorial team:

The concept of "medical cannabis" has been heavily publicised recently, both in the United States, Australia and in New Zealand. This country has one of the highest rates of cannabis use in the world,[1] and approximately 5% of people aged over 15 years report using cannabis for medical purposes.[2] Patients considering using cannabis illegally for a medical purpose should, instead, be offered approved medicines that have evidence of safety and efficacy.

Robust clinical trials using cannabis to treat medical conditions are lacking. Δ^9-tetrahydrocannabinol (THC) has traditionally been regarded as the psychoactive ingredient of cannabis. However, cannabis contains approximately 70 other different compounds, any one of which may be pharmacologically active.[3] Furthermore, the levels of THC can vary widely between strains of cannabis. These variables make it difficult to interpret research assessing the efficacy of cannabis for medical purposes and creates problems when considering how a non-standardised product should be dosed.[3, 4]

Observational studies show long-term cannabis use is associated with adverse social and financial consequences,[5] and cannabis use increases rates of psychosis.[6] As with recreational cannabis use, medical cannabis use could also lead to other serious adverse effects, such as motor vehicle accidents.[7] It is therefore reasonable to ask whether cannabis has any place in medical practice given the availability of other medicines which have been tested in clinical trials and met regulatory standards.

Unlike cannabis plants, manufactured medicines can be produced to a highly consistent standard, allowing specific, evidence-based doses to be prescribed.[3, 8, 9] There is one cannabinoid approved for use in New Zealand, Sativex, a combined cannabidiol/THC oromucosal spray, for the treatment of severe spasticity associated with multiple sclerosis. A Cochrane review and a major meta-analysis, both published in 2015, found moderate quality evidence that cannabinoids (as opposed to cannabis) may be useful for the treatment of chronic pain, including neuropathic pain, and spasticity associated with multiple sclerosis.[10, 11] There is also moderate quality evidence that cannabinoids may be effective antiemetics for adjunctive use in chemotherapy or to assist weight-gain in patients with HIV.[10, 11] There is low quality evidence in support of other uses such as reducing anxiety or improving sleep.[10, 11] Adverse effects commonly associated with cannabinoid use include dizziness, dry mouth, nausea and vomiting, fatigue, sedation, dysphoria and hallucinations.[11]

Medical use should not be used to promote legalisation

Cannabis is now being used in the United States for the treatment of medical conditions as diverse as epilepsy, post traumatic stress disorder, Crohn's disease, sickle cell disease, psoriasis, and amyotrophic lateral sclerosis, with neither clear evidence of effectiveness, nor the same robust evaluation required of other medicines.[3] As a result the medical use of cannabis has become muddled with the issue of legalisation of cannabis. An editorial published in JAMA, in 2015, commented:[3]

> *[if the] "initiative to legalize medical marijuana is merely a veiled step toward allowing access to recreational marijuana, then the medical community should be left out of the process, and instead marijuana should be decriminalized. Conversely, if the goal is to make marijuana available for medical purposes, then it is unclear why the approval process should be different from that used for other medications."*

Both Australia and the United States relaxed legislation over the availability of cannabis for medicinal purposes in 2015. The New Zealand government has indicated wider access to cannabis for medical purposes may be granted once appropriate clinical trials have been conducted and the trial products approved, although there is no indication when this might be.

References

1. Degenhardt L, Chiu W-T, Sampson N, et al. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. PLoS Med 2008;5:e141. doi:10.1371/journal.pmed.0050141
2. Pledger M, Martin G, Cumming J. New Zealand Health Survey 2012/13: characteristics of medicinal cannabis users. New Zealand Medical Journal;129:29–40.
3. D'Souza DC, Ranganathan M. Medical Marijuana: Is the Cart Before the Horse? JAMA 2015;313:2431–2. doi:10.1001/jama.2015.6407
4. Vandrey R, Raber JC, Raber ME, et al. Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products. JAMA 2015;313:2491–3. doi:10.1001/jama.2015.6613
5. Fergusson DM, Boden JM. Cannabis use and later life outcomes. Addiction 2008;103:969-976-978. doi:10.1111/j.1360-0443.2008.02221.x
6. Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. Addiction 2005;100:354–66. doi:10.1111/j.1360-0443.2005.01001.x
7. Poulsen H, Moar R, Troncoso C. The incidence of alcohol and other drugs in drivers killed in New Zealand road crashes 2004-2009. Forensic Sci Int 2012;223:364–70. doi:10.1016/j.forsciint.2012.10.026
8. Aamir T. New Zealand doctors should be allowed to prescribe cannabis for pain: No. J Prim Health Care 2015;7:160–1.
9. Hardy PA. New Zealand doctors should be allowed to prescribe cannabis for pain: Yes. J Prim Health Care 2015;7:158–9.
10. Smith LA, Azariah F, Lavender VTC, et al. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database Syst Rev 2015;11:CD009464. doi:10.1002/14651858.CD009464.pub2
11. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA 2015;313:2456–73. doi:10.1001/jama.2015.6358

Oxycodone prescribing in the community: What can primary care do?

Dear Editor,

Re: Oxycodone update, prescribing report (Mar, 2016)

The pattern of opioid use in hospital, particularly in orthopaedic services, has not changed during 2015. The predominant discharge analgesia is oxycodone, or occasionally tramadol. Until hospital prescribing changes, we in primary care are unable to alter the statistics at all. Now that the eGFR [estimated glomerular filtration rate] is increasingly used as a predictor of problems, there is a reluctance to use morphine at all, especially in the elderly post fracture NOF [neck of femur fracture] etc.

Dr Brian Ross, General Practitioner
Pukekohe

Response from bpac^{nz} editorial team:

Most prescribing of oxycodone is initiated in hospitals and general practitioners have limited opportunity to influence secondary care prescribing. However, oxycodone use in the community does need to be minimised; the current opioid epidemic in the United States is a cautionary tale. In the United States pharmaceutical opioids now kill more people than firearms or traffic accidents,[1] and more than the combined death rates from heroin and cocaine overdoses.[2]

General practitioners can take action by evaluating the ongoing need for strong analgesia in patients discharged from hospital, and discontinuing oxycodone when it is no longer required. If patients are discharged from hospital with a strong opioid, the prescription should be for a short time period and the patient should have a treatment plan for tapering their analgesic use. Clinicians in primary care do not need to provide repeat prescriptions for strong opiods for all patients discharged from hospital. The decision to prescribe oxycodone, or another strong opioid, should balance the predicted net benefits from treatment against the risks of adverse effects, misuse and addiction.

Renal impairment is a factor to consider when prescribing opioids. The effects of any opioid, including oxycodone, may be increased and prolonged for patients with renal impairment. For patients with mild renal impairment, dose reduction is advised. In patients with severe renal impairment (eGFR < 10 mL/min/1.73 m^2), both morphine and oxycodone should be avoided due to accumulation of active metabolites, which can lead to opioid toxicity; fentanyl is regarded as the safest strong opioid for patients with renal impairment.

References

1. Rudd R, Aleshire N, Zibbell J, et al. Increases in drug and opioid overdose deaths - United States, 2000 - 2014. 2016.www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm (Accessed May, 2015)
2. National Institute on Drug Abuse. Overdose death rates. 2015.www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates (Accessed May, 2015)

We value your feedback. Write to us at:
Correspondence, PO Box 6032, Dunedin
or email: editor@bpac.org.nz