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Title page

A commentary paper for publication

Title: Fish oil for rheumatoid arthritis: A Home Medicine Review initiative

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Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition that affects about 2% of the Australian population [1]. In RA, the overproduction of inflammatory mediators such as tumour necrosis factor, interleukin-1, 6, 8 and cytokines, causes chronic inflammation and pain in joints [2]. There is growing evidence of the benefits of omega-3 long chain polyunsaturated fatty acids found in fish oil in reducing chronic inflammation associated with RA [3]. Fish oil contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that compete with inflammatory precursors [3]. Clinical studies and independent therapeutics guidelines [4-7] suggest to use at least 2.7g of EPA in addition to DHA present in fish oil per day for the pharmacological management of RA. Human studies have shown that fish oil can significantly reduce inflammatory mediators, although this appears to be most significant at when the dose of EPA+DHA is above ≥ 2.7 g daily suggesting that there is a threshold dose required for the effectiveness of fish oil in reducing inflammation [2]. Fish oil has also been shown to reduce the use of nonsteroidal anti-inflammatory drug (NSAID) consumption [2, 3] and thus the risk of well-known NSAID adverse effects such as gastrointestinal bleeding or exacerbation of heart failure [8].

Use of complementary medicines including fish oil supplements is becoming increasingly popular in many countries including Australia [9]. Fish oil supplements can be purchased over the counter (OTC) without supervision of health practitioners and there are a plethora of fish oil products available in varying strengths. Patients are highly influenced by the media and the internet which often promote self-medication behaviour [10]. Patients who do self-medicate with fish oil for their RA, may not be aware or have poor health literacy of the recommended dose to achieve an anti-inflammatory response and take one or two capsules of fish oil regardless of the strength of the omega-3 component of capsules, which is generally insufficient for anti-inflammatory effects of fish oil [5]. Under-dose treatment with fish oil supplements in RA is likely to be ineffective, and may cause a financial burden to patients with RA, while overdose may generate a risk of possible nutrient-drug interactions or adverse effects. Community pharmacies are of the main suppliers of complementary medicines including fish oil products in Australia [9], however, this does not mean

that patients seek information or advice from pharmacist when they purchase fish oil products. In fact, the dose of fish oil products used at the consumer level for different medical conditions such as RA is unknown.

Home Medicine Review, a clinical service provided by community pharmacies

Pharmacists in Australia have progressively extended their roles from traditional supply of medicines to more clinical roles through patient-orientated government funded services, including Home Medicines Review (HMR) [11]. HMR is a government-funded program in Australia that allows accredited pharmacists to review patients' medications and make recommendations to their general practitioners [11]. HMR processes involves providing patients' education and conduct an assessment of prescribed and OTC medicines including the complementary medicines used by patients which may not be known to the general practitioners (GPs) [11]. HMR is designed to be an effective tool to address suboptimal use of medications including prescription and complementary medications.

We retrospectively investigated a de-identified sample of HMRs conducted by pharmacists for patients with RA to identify the dosage of fish oil used in this population and recommendations of pharmacists towards the use of fish oil to assess the potential impact of HMR in optimising medication management in patients with RA and using fish oil supplements.

These patients were referred from GPs to accredited pharmacists to conduct HMR service on the basis of standard referral criteria [11]. HMRs were conducted by 7 accredited pharmacists between 2012 and 2014. Initially 290 de-identified HMRs were screened in which 24 patients were diagnosed with RA by GPs. From these, 8 HMR reports were identified and included in this study in which, patients with RA used regular fish oil supplements. The mean age of the patients was 75 years (65-80). The mean number of medical conditions listed in the HMR referrals by GPs was 8 (6-10) per patient and the mean number of medications listed on referral was 16 (8-26) indicating of polypharmacy in the study sample. Interestingly, all patients with RA used sub-therapeutic doses of

fish oil. Analysing the recommendations of pharmacists in HMR reports for these patients, showed that in 75% (n=6) of these cases, pharmacists identified sub-therapeutic doses of fish oil. However, only in half of the cases (n=4) cases, pharmacists made clear recommendations to the GPs to either increase the dose to 2.7g of EPA+DHA (n=3, %38) or to cease the use of fish oil supplement due to the lack of efficacy at the administered dose (n=1; 13%). Box 1 and Box 2 provide 2 examples of patients using insufficient doses of fish oil to treat their RA and other medication-related issues identified during the HMR, highlighting the benefits of a comprehensive medication review by a pharmacist.

Although this study had a small sample size and findings may not be generalizable to the larger population, the study highlights the role of pharmacists in promoting evidence based use of complementary medicines and warrants further investigation. Given the high levels of self-medication with OTC and complementary medicines are reported in Australia [12], pharmacists play a key role in educating consumers about the appropriate use of complementary medications. HMRs provide a unique opportunity for pharmacists to interact with patients in their residence, observe their medications and identify potential medication related problems.

Health care providers especially pharmacists and GPs need to be more involved in monitoring the use of complementary medicines in patients with chronic diseases. HMR may have a key role in promoting evidence based use of complementary medicines.

Box 1

Case one

A woman in her 70's with RA, osteoarthritis, ischemic heart disease, irritable bowel syndrome and hypercholesterolemia was referred to a pharmacist for a HMR. The patient was treated with the following prescribed medications from her general practitioner:

- leflunomide 10mg daily
- paracetamol extended release 665mg, two tablets three times a day for RA associated pain.
- Aspirin 100mg
- verapamil 180mg
- atorvastatin 20mg
- omeprazole 20mg
- vitamin D 2000 IU
- calcium 600mg and
- cranberry capsule 10g daily.

At the HMR interview, the pharmacist identified that the patient also takes several complementary medicines including:

- krill oil 500mg
- multivitamin tablet
- honey garlic in base of apple cider vinegar capsule
- antacid liquid
- expectorant cough mixture
- and a product containing fish oil 750mg magnesium 150mg, vitamin E 50IU, folic acid 250mcg and hawthorn fruit 1g daily

The patient was using the product containing fish oil with the perception that it was beneficial for her RA symptoms and general health. The patient reported she had had a prior reaction to methotrexate (unable to tolerate) and preferred to manage her RA-associated pain with using complementary medicines. The patient used krill oil as she believed krill/fish oil might improve her RA symptoms; however, she was unaware of the required dosage. The patient disclosed to the pharmacist that she did not discuss her complementary medicine use with her GP and asked enquired whether krill oil is preferred over fish oil for RA. Following the HMR, the pharmacist reported to her GP that the current dose of fish oil is unlikely to provide any benefits for her RA

symptoms and recommended to increase the dose to 2.7g of EPA+ DHA. The pharmacist also identified the interaction between garlic and aspirin, leading to increased antiplatelet effects of aspirin and recommended to review the clinical need for taking multiple complementary medicines including garlic, magnesium, krill oil, multivitamin, calcium and cranberry with a view of a potential cessation of those medicines.

1

Box 2

Case two

A man in his 70's with RA, degenerative disc disease, gout, hypertension, hypercholesterolaemia, and chronic pain was referred to a pharmacist for a HMR. His medications included:

- meloxicam 7.5mg daily
- fish oil 1g containing 300mg EPA+DHA (purchased over the counter) for RA,
- tramadol 100mg twice daily
- oxycodone/naloxone 10mg/5mg for chronic pain,
- candesartan/hydrochlorothiazide 16mg/12.5mg,
- atorvastatin 20mg
- allopurinol 300mg daily.

The patient's main concern was chronic pain associated with RA and degenerative disc disease. Following the HMR, the pharmacist reported to the patient's GP that:

- (i) the current dose of fish oil is unlikely to provide any benefits for RA symptoms and recommended to either cease it or to increase the dose to 2.7g of EPA+ DHA.
- (ii) the patient often takes oxycodone/naltrexone 10mg/5mg up to four times a day to achieve adequate pain relief whereas it was prescribed to be taken only once daily by the referring GP and the GP was unaware of the dose increase;
- (iii) meloxicam can worsen blood pressure control, increases cardiovascular risk in the elderly, and the combination of meloxicam, candesartan and hydrochlorothiazide can precipitate renal failure. The pharmacist recommended to cease meloxicam and review RA treatment/pain management.

2

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