European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 06, Issue 01, 2019

Impact of OTC Purchase and Utilization of Pain Killers in Rheumatoid Arthritis

ARCHANA DHYANI,
Department of Pharmacy, Graphic Era Hill University,
Dehradun, Uttarakhand, India 248002

Abstract
Pain may be alleviated externally using topical therapies. It's true that topical pain relievers are effective. A lot of the time they also cause a thermal or a thermal sensation on the skin. The lack of systemic absorption means that topical therapies are safer than oral drugs. There are a variety of over-the-counter (OTC) topical creams, sprays, and gel pain relievers available for the treatment of arthritis and other types of physical pain. Both nonsteroidal anti-inflammatory drugs (NSAIDs) and capsaicin, the chemical responsible for chilli peppers' spiciness, may be used. Yet, NSAIDs are not without hazards and adverse effects. Prostaglandins are involved in a variety of processes in addition to pain. Yet, since NSAIDs lower prostaglandins in the body, the stomach lining may become more susceptible to injury from acid. Causes of stomach distress, ulcers, and internal bleeding may result from this. Additional potential NSAID side effects include hives, wheezing, which may be harmful for those with asthma; changes in renal function; and a rash. This study takes an indepth look at the use of pain killers in rheumatoid arthritis.
Keywords: Protect, Prostaglandins, Damage, Wheezing, Vulnerable.

Introduction:

Symptoms of rheumatoid arthritis may be managed with anti-inflammatory drugs including ibuprofen and steroids. Yet, they are not effective in protecting the joints. They function well as a stopgap measure for severe pain until disease-modifying medicines takeOne of the best over-the-counter treatments for osteoarthritis pain is nonsteroidal antiinflammatory medicines (NSAIDs), "say the American College of Rheumatology and the Arthritis Foundation. In addition to alleviating pain, NSAIDs also have anti-inflammatory effects."

Options include:

i. "ibuprofen (Motrin) tablets for all types of OA"
ii. "Creams and ointments containing NSAIDs for OA of the knee and hand"
iii. "naproxen (Aleve)"
iv. "aspirin"
v. "nabumetone (Refalen)"

Pain and inflammation may be alleviated with the help of NSAIDs since they act by lowering levels of chemicals in the body called prostaglandins. This helps alleviate discomfort and decrease joint swelling and inflammation (Van Walsem et. al., 2015). Nonsteroidal anti-inflammatory drugs (NSAIDs) also lessen blood coagulation. If a person is at a high risk for a heart attack, for instance, they may take aspirin to thin their blood. Yet, excessive blood-thinning increases the danger of bleeding or bruising. Another over-the-counter (OTC) medicine useful for arthritic pain management is acetaminophen (Tylenol). The brain's perception of pain is decreased, allowing this medication to relieve discomfort. While it may alleviate discomfort, it will not diminish joint inflammation. So, the ACR/AF only gives their stamp of approval if one cannot use

nonsteroidal anti-inflammatory drugs. When used in excess, acetaminophen may cause serious side effects, such as a skin rash (Da Costa et al, 2017). Liver damage may occur through long-term use of high doses or from mixing it with alcohol. Yet it's safe to use when expecting a child. Herbs and supplements were used by some people to give treatment to OA pain, like:

(i) Vit-D
(ii) FishOil
(iii) "glucosamine"

Nevertheless, they are not recommended by professionals since there is little data to prove their efficacy and some may combine with other medications or induce undesirable side effects.

Dealing with Pain in Arthritis : In OA, the articular cartilage gradually deteriorates, leading to subchondral bone remodelling, osteophyte development, and secondary irritation of synovial membranes.Various variables combine to cause the disease's primary symptom—pain. Compressive stresses and hypoxia may trigger these new neurons, producing pain even after inflammation has gone. This suggests that innervation and vascularization of the articular cartilage may be involved. Some OA patients have a deep joint pain that has been linked to the innervation of the cartilage in the joint and angiogenesis. Patients with osteoarthritis have been shown to have lower pain limits than controls at the forehead, and a non-painful region of the body unaffected by OA, when subjected to quantitative sensory testing for both mechanical and thermal pain. These results imply that the pain associated with OA is centrally mediated as well. Multiple brain areas involved in processing OA pain have been found via fMRI (functional magnetic resonance imaging) research, highlighting the complexity of OA pain processes.

The elderly population across the world has a high rate of OA. Long-term analgesia is particularly difficult for the elderly, a fact that is not often acknowledged in the relevant literature or recommendations. There is a dearth of data regarding the old population since randomised clinical studies seldom include them, and even fewer include senior patients of different races and ethnicities. Comorbidities are common among the elderly, which might raise the risk of interactions between medications and reduce the treatment options available to the patient. It is important to take into account age-related changes in medication sensitivities while treating older patients, however it is difficult to provide universally applicable recommendations due to the diversity of the geriatric OA population. Opioids have shown useful in the older population, but their usage requires thorough clinical monitoring.

Extreme Pain in Progressive Disorders : Periods of disease activity are interspersed with remission in RA, which is a progressive condition. Patients may have moderate to severe pain that is either constant or intermittent. Cartilage & underlying bone are destroyed by the inflammatory process that characterises RA. Since the joint capsule or synovium are highly innervated, even little stimulation or motion of the afflicted joint may cause severe pain. Synovial fibroblasts and other resident non-immune cells help the immune system orchestrate the local inflammatory response. Multiple substances are released as a result of local inflammation. These include cytokines that promote inflammation, histamines, and prostaglandin E2, among others. The shift in cytokines causes sensitization of peripheral nociceptors. Central sensitization is triggered by cellular cascades. Pressure pain thresholds are lower in RA patients compared to healthy controls,

indicating further that RA patients' brains perceive pain differently. Increased cortical reactions to painful stimuli in RA patients may indicate cellular alterations that alter the way pain signals are processed. There is still much to learn about the complex interplay between peripheral sensitization or inflammation in rheumatoid arthritis patients.

Arthritis-Related Pain - Current Analgesics: Rheumatologists seek to alleviate their patients' suffering by understanding the fundamental asset pathophysiological mechanisms of inflammatory diseases like rheumatoid arthritis. However, rheumatologists are starting to think outside the box when it comes to pain treatment as a result of our improved knowledge of pain processes and rising respect for pain control. It is less obvious how to control the centralised pain processes in both of these patient groups, whereas pharmaceutical therapy for people with fibromyalgia increasingly targets central pain mechanisms. As a result, it has been suggested that "pain-modifying analgesic drugs" replace traditional analgesics as the primary means by which practitioners manage arthritic pain. The following pharmacological medications are often utilised for pain management in osteoarthritis (OA) and osteoarthritis (RA) patients. It's important to remember that non-pharmaceutical methods may be included into any therapy plan.

To understand the purchase of over-the-counter drugs sold without a prescription several studies have been conducted. Common medications bought are:

Celecoxib, diclofenac, etoricoxib, ibuprofen, and naproxen are all of which are nonsteroidal antiinflammatory drugs (NSAIDs) that help alleviate joint discomfort. Around 15% of those who use them report an improvement in their symptoms, according to the research (Derry et al., 2016)4. Many variables, including the medicine and dosage, will influence the potential for adverse reactions and problems.

When compared to other NSAIDs, celecoxib and etoricoxib are safer for the stomach. The risk of cardiovascular disorders like heart attacks may be somewhat increased by using NSAIDs, with the exception of acetylsalicylic acid (the substance in treatments like Aspirin). Naproxen has the lowest risk of this side effect, making it the best NSAID for those with rheumatoid arthritis and heart problems.

Long term usage of NSAIDs has been linked to the development of stomach ulcers. One's upper abdomen may hurt as a result of them. After eating, when stomach acid levels are highest, the agony is at its worst. Often patients withstomach ulcers do not even know they have them until they develop major consequences like gastrointestinal haemorrhage (DGRh, 2019)5.

Inclusion Criteria for Rheumatoid Arthritis Pain Killer Usage : Higher Risk of Complications:

Those who: have a history of stomach ulcers or bleeding; have a weak immune system; smoke;

i. Are older than 65,
ii. Having a preexisting ailment, particularly a digestive disorder like Crohn's disease or ulcerative colitis,
iii. Have a history of stomach problems such as gastritis (inflammation), ulcers, or bleeding,
iv. Suffer from a Helicobacter pylori infection,
v. Consume excessive amounts of alcohol,
vi. Anticoagulants like warfarin or acetylsalicylic acid, which are used to treat cardiac conditions, (vii) do anything like antidepressant medication selective serotonin reuptake inhibitor (SSRI),
vii. Either use corticosteroids (or "steroids"),

viii. Use a combination of anti-inflammatory medications to combat discomfort.

Those with renal problems may also have adverse effects from NSAIDs. As a result, NSAIDs should be taken sparingly and not continuously, i.e., only for short-term relief of severe pain. Avoid exceeding the maximum recommended daily dosage and utilise the lowest effective dose. Using NSAIDs alongside medication meant to protect the lining of the stomach may significantly reduce the risk of issues affecting the gastrointestinal system. Proton pumpinhibitors like omeprazole and pantoprazole are among them (Fidahic et al, 2017)6. You may also try a topical lotion or cream with diclofenac or ibuprofen on the aching joint. As compared to taking pills, the potential for adverse consequences is much reduced in this scenario. Only under a doctor's watchful eye should any drug be consumed.

Acetaminophen (paracetamol), although effective in relieving pain, does nothing to reduce inflammation. Evidence suggests it is not as effective as nonsteroidal antiinflammatory drugs (NSAIDs) for relieving the pain associated with rheumatoid arthritis (Hazlewood, van der Heijde and Bombardier, 2012)7. Liver and renal failure might occur with higher dosages. According to the directions on the box, adults shouldn't take more than 4 grammes (4,000 milligrammes) daily. This is the equivalent of eight 500 mg acetaminophen pills. It is also suggested that at least six hours pass between dosages. Thus, the maximum recommended daily dose is two 500 mg tablets spaced every six hours.

Adverse Impact of OTC Purchases : Most of the dangers associated with using nonsteroidal antiinflammatory drugs (NSAIDs) are dose- and time-dependent, pharmacological. Even though there is a lot of conjecture regarding the potential dangers of low-dose "over-thecounter" NSAIDs, very little is known about how these drugs are actually used. The same holds true for the majority of nonsteroidal antiinflammatory drugs available with a doctor's prescription.

Risk assessments for these drugs may not be applicable to real-world usage, since they were developed in clinical trials and observational studies that did not include OTC use. It is important to note that cyclo-oxygenase (COX) inhibitors, of which what are known as 'coxibs' are a group, are used for a wide range of conditions as well as types of use, from extremely short-term, periodic administration at low dosages in prevalent discomforts like colds and influenza, migraines, or painful periods to a long-term ongoing administration at elevated levels in long-term inflammatory conditions like rheumatoid arthritis.

Although NSAIDs have a wide variety of therapeutic and adverse effects, which is consistent with the widespread distribution of prostaglandins, gastrointestinal and cardiovascular adverse reactions have been of primary concern for NSAIDs in recent years; for both of these, the dose and durationdependence of the risk has been demonstrated. Certain NSAIDs are available solely via prescription, while others may be purchased "over-the-counter" (OTC) under a variety of brand names and packaging sizes. While NSAIDs are often prescribed, little is understood about their actual use. Real-world POM NSAID usage is likely to be less continuous and longer duration than in randomised clinical studies, especially for chronic illnesses. In this case, it would explain why the actual occurrence rates are lower than predicted. Often, OTC NSAIDs are used by younger patients, at lesser dosages, for shorter periods of time, and for different reasons than POM NSAIDs.

Healthier Alternatives to NSAID Use : Previous research has shown that NSAID users

are disproportionately young, with an average age of 40 for OTC users and 47 for POM users. In both groups, the rates of coexisting chronic conditions were low, as would be anticipated given the ages of the people who used OTC and prescription drugs. There were fewer coexisting illnesses in the younger OTC users compared to the older POM users. Most of these low-risk individuals will only be exposed to NSAIDs for a short period of time, therefore the likelihood of a substantial influence on cardiovascular risk or interaction with cardiovascular medicines seems minimal.

Some of the alternatives can be listed as:

i. Walking: A treadmill (without an inclination) might be utilised for those who have trouble keeping their balance. Walking ata moderate speed is a great low-impact workout that can be done anywhere.
ii. In order to gradually increase strength, riding a stationary bike on the easiest setting is recommended. Riding a bike around the neighbourhood is a great way to get some exercise and avoid the stress of driving.
iii. Freestyle swimming is a good water exercise since it offers a cardio and strength training workout at a moderate intensity. Water walking has several health benefits, including reducing joint stress and strengthening muscles. In many cases, this helps reduce hip discomfort and restores normal movement.
iv. Yoga: When practised regularly, it may help strengthen muscles, reduce discomfort, and increase joint flexibility. If you're experiencing pain in your hips during yoga, tell your teacher so they can modify the pose for you. The best way to learn is to enrol in an introductory course.
v. Tai chi's gentle, flowing motions may help ease arthritic pain and improve balance. Stress may be reduced in a healthy and natural way using tai chi.
vi. Strength training is a great way to reduce stress on your hip joints and enhance your balance. No more than two sessions of strength training per week are recommended to build muscles

There are a number of indications that warn and can help relieve OA hip pain

i. Pay attention to how body reacts to actions and modify them accordingly.
ii. Maintain a low intensity level and focus on strengthening muscles around hips.
iii. Increased discomfort prompts one to take a break for a while. Overusing the hip might be the cause of joint discomfort that persists long after movement is stopped.
iv. Try to get in some walks whenever possible throughout the day to keep metabolism up.
v. When hip pain strikes, many people go for nonprescription anti-inflammatory drugs.
vi. Get enough sleep.
vii. Take care of weight; being overweight is an unmanageable nuisance.
viii. Participate in a health club or take an exercise class to keep your mind and body engaged and productive.

Most healthcare databases have the several shortcomings, like:

i. Lack of information on pharmacological indications and recommended dosage
ii. A scarcity of data about comorbidities, with the exception of long-term disorders.

In nations where the dosage is determined by the prescription, this may be a serious problem. Products in France are sold in boxes containing a certain number of pills of a known potency. Total drug distribution volume (DDD) may be calculated with high accuracy. This allows us to extrapolate the more general indications for the medication's use; for example, it's highly unlikely that a prescription issued for only a

few days' worth of treatment over a duration of two years is for rheumatoid arthritis or osteoarthritis, but rather for episodes of acute pain. In contrast to continuously used drugs like antiepileptics, antihypertensives, or lipidlowering medications, the time of usage in relation to the time of administration may be inconsistent for NSAIDs since they are symptom-relieving dugs.

Both nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol are widely used, highly recommended, and efficient pain relievers. Some people, such as the elderly and those with preexisting conditions including renal, gastrointestinal, and cardiovascular illness, may be unable to safely use them. Problems with tolerance and major side effects have also been linked to the use of NSAIDs at high dosages and for extended periods of time to treat moderate to severe pain. As a result, they don't play much of a role in relieving the chronic pain caused by OA and RA.

The hepatic damage is of particular significance since paracetamol is a "hidden" element in many over-the-counter medications and other combination products, and because it has been linked to toxicity at higher levels. Paracetamol is often used in fixed-dose combinations since modest dosages of both the medication and the additional agent are available. Patients should still be warned about the quantity of paracetamol in any combination medications they may be given, even if they are administered a lower dosage of paracetamol than is typically used.

Paracetamol fixed-dose combinations provide a multimechanistic analgesic strategy, which may be useful in treating the pain associated with rheumatoid arthritis and osteoarthritis. The moderate to severe pain associated with osteoarthritis and rheumatoid arthritis may be effectively managed with fixed-dose mild opioid/paracetamol combination solutions. In the treatment of OA and RA pain, tramadol may be useful as an opioid component in combos due to its dual opioid and nonopioid modes of action.

Pain associated with arthritis often comes in waves, with some patients experiencing severe pain followed by intervals of relief. It is recommended that a low-dose fixed-dose combo medication be considered as the principal analgesic for the management of long-term arthritic pain since it provides safe and satisfactory multimechanistic pain relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) should only be used to treat severe, acute inflammation. This is in contrast to the conventional treatment plan, in which patients undergo long-term nonsteroidal anti-inflammatory drug (NSAID) therapy and then switch to opioids for flare-related pain. Analgesic spectrum expansion, synergistic analgesia benefits, and a better ratio of effectiveness to side effects are all possible outcomes of utilising a low-dose opioid combo medication.

Conclusions

Over-the-counter (OTC) NSAIDs are used in ways that make sense, given their traditional pain indications. Both OTC and prescription NSAID purchases in this research were much lower than what is typically supplied to patients in clinical studies. Much of the dangers associated with NSAIDs come from the fact that people seldom purchase the quantities used in clinical studies. These use patterns should be considered when extrapolating the outcomes of clinical studies to the actual use and dangers of NSAIDs in the real world. Therefore more real-world research is required to precisely describe the true dangers of low-dose OTC or prescription NSAIDs.

Reference

1. American Geriatric Society Panel on the Pharmacological Management of

Persistent Pain in Older Persons. Pharmacological Management of Persistent Pain in Older Persons. *J Am Ger Soc.* 2009;57(8):1331–46.

2. Ashraf S, Wibberley H, Mapp P, Hill R, Wilson D, Walsh D. Increased vascular penetration and nerve growth in the meniscus: a potential source of pain in osteoarthritis. *Ann Rheum Dis.* 2011;70:523–9.
3. Baker K, Grainger A, Niu J, et al. Relation of synovitis to knee pain using contrast-enhanced MRIs. *Ann Rheum Dis.* 2010;69(10):1779–83.
4. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA et al. Vascular and upper gastrointestinal effects of nonsteroidal anti-inflammatory drugs: metaanalyses of individual participant data from randomised trials. Lancet 2013; 382(9894): 769-779.
5. Blin P, Lassalle R, Dureau-Pournin C, Ambrosino B, Bernard MA, Abouelfath A, Gin H, Le Jeunne C, Pariente A, Droz C, Moore N. Insulin glargine and risk of cancer: a cohort study in the French National Healthcare Insurance Database. Diabetologia. 2012;55:644–653.
6. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med. 2000;343:1520–1528.
7. Bonnet C, Walsh D. Osteoarthritis, angiogenesis and inflammation. *Rheumatology.* 2005;44:7–16.
8. Da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet 2017; 390(10090): e21-e33.
9. Dachverband der Deutschsprachigen Wissenschaftlichen Osteologischen Gesellschaft (DVO). Prophylaxe, Diagnostik und Therapie der Osteoporosebeipostmenopausalen Frauen und bei Männern (Leitlinie). AWMFRegisternr.: 183-001. 2017.
10. Depont F, Fourrier A, Merliere Y, Droz C, Amouretti M, Begaud B, Benichou J, Moride Y, Blin P, Moore N. The CADEUS study: methods and logistics. Pharmacoepidemiol Drug Saf. 2007;16:571–580.
11. Derry S, Conaghan P, Da Silva JA, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2016; (4): CD007400.
12. Deutsche Gesellschaft fürRheumatologie (DGRh). Management der frühenrheumatoiden Arthritis (S3-Leitlinie). AWMF-Registernr.: 060-002.December 18, 2019.
13. Farrell M, Gibson S, McMeeken J, Helme R. Pain and hyperalgesia in osteoarthritis of the hands. *JRheumatol.* 2000;27:441–7.
14. Fidahic M, JelicicKadic A, Radic M, Puljak L. Celecoxib for rheumatoid arthritis. Cochrane Database Syst Rev 2017; (6): CD012095.
15. Goldring M, Goldring S. Osteoarthritis. *J Cell Physiol.* 2007;213:626–34.
16. Hazlewood G, van der Heijde DM, Bombardier C. Paracetamol for the management of pain in inflammatory arthritis: a systematic literature review. J RheumatolSuppl 2012; 90: 11-16.
17. Kosek E, Orderberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with

painful osteoarthritis before, but not following, surgical pain relief. *Pain.* 2000;88(1) :69–78.

18. Laharie D, Droz-Perroteau C, Benichou J, Amouretti M, Blin P, Begaud B, Guiard E, Dutoit S, Lamarque S, Moride Y, Depont F, Fourrier-Reglat A, Moore N. Hospitalizations for gastrointestinal and cardiovascular events in the CADEUS cohort of traditional or Coxib NSAID users. Br J Clin Pharmacol. 2010;69:295–302.
19. Lee Y, Nassikas N, Clauw D. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arth Res Ther.* 2011;13:211–21.
20. Mandl L. Treating the pain of osteoarthritis-where do we go from here? *J Rheumatol.* 2011;38 (8):1535–7.
21. Martin-Latry K, Begaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! Pharmacoepidemiol Drug Saf. 2010;19:256–265.
22. Mease P, Hanna S, Frakes E, Altman R. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. *J Rheumatol.* 2011;38:1546–51.
23. Moore N, et al. Comment on 'Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use' Tramer. Pain. 2000;85:169–182. Pain 2001; 91: 401–2.
24. Moore N, Van Ganse E, Le Parc J, Wall R, Schneid H, Farhan M, Verrière F, Pelen F. The PAIN study: paracetamol, aspirin and ibuprofen new tolerability study. A largescale, randomized clinical trial comparing the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. Clin Drug Invest. 1999;18:89–98.
25. Moore N. Place of OTC analgesics and NSAIDs in osteoarthritis. Inflammo pharmacology. 2003;11:355– 362.
26. O'Driscoll S, Jayson M. Pain threshold analysis in patients with osteoarthritis of the hip. *BMJ.* 1974;3:714–5.
27. Ofman JJ, Maclean CH, Straus WL, Morton SC, Berger ML, Roth EA et al. Metaanalysis of dyspepsia and nonsteroidal antiinflammatory drugs. Arthritis Rheum 2003; 49(4): 508-518.
28. Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E et al. Prevention of NSAIDinduced gastroduodenal ulcers. Cochrane Database Syst Rev 2002; (4): CD002296
29. Seed S, Dunican K, Lynch A. Osteoarthritis: a review of treatment options. *Geriatrics.* 2009;64(10):20–9.
30. Silverstein FE, Faich G, Goldstein JL, SimonLS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000;284:1247–1255
31. Sofat N, Ejindu V, Kiely P. What makes osteoarthritis painful? The evidence for local and central pain processing. *Rheumalogy.* 2011;50:2157–65.
32. Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model

applied to chronic NSAID use. Pain. 2000;85:169–182.

33. Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefitrisk comparing diclofenac to other traditional non-steroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network metaanalysis. Arthritis Res Ther 2015; 17: 66.