Volume 7, Number 3, December 2024

The Journal of Indonesian Orthopaedic & Traumatology

journal homepage: https://journal.indonesia-orthopaedic.org

Review Article

Conservative Management and Surgical Indications for Rotator Cuff Tears: Review

Adrian Djatikusumo[1], Aivi Mujono[1,4], Edlyn Amadea[1,3], Erica Kholinne[2,3]

[1]Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia
[2]Faculty of Medicine, Universitas Trisakti, Jakarta
[3]Department of Orthopedic Surgery, St. Carolus Hospital, Jakarta, Indonesia
[4]RSUD dr. Hendrikus Fernandez Larantuka, East Nusa Tenggara, Indonesia

Article History :
Submission: May 11,2024
Revision: August 9, 2026
Accepted: August 14, 2026

Keywords:
Conservative treatment
Rotator cuff
Shoulder pain
Surgical treatment

Corresponding Author:
Adrian Djatikusumo, MD
adriandksm@gmail.com

Abstract

Introduction: Shoulder pain is a common musculoskeletal complaint with various causes, including rotator cuff injuries. Conservative management is generally considered the first-line treatment for many patients with rotator cuff tears and includes physical therapy, activity modification, analgesic medications, subacromial corticosteroid injections, and other emerging therapies. This literature review aimed to evaluate the effectiveness and mechanisms of currently available conservative treatment options for rotator cuff injuries.

Methods: A literature search was conducted for studies evaluating conservative management of rotator cuff injuries. Data regarding treatment modalities, clinical outcomes, pain reduction, functional improvement, and adverse effects were extracted and reviewed qualitatively.

Results: The reviewed literature suggests that conservative management can provide meaningful improvements in pain and shoulder function in patients with rotator cuff injuries. Physical therapy remains a cornerstone of treatment, particularly exercises aimed at restoring shoulder strength, mobility, and function. Analgesics and subacromial corticosteroid injections may provide short-term symptom relief, while emerging biological and nonoperative therapies show varying degrees of efficacy. Treatment outcomes may depend on factors such as tear characteristics, patient age, symptom duration, and adherence to rehabilitation.

Conclusion: Conservative management is an effective initial treatment strategy for many patients with rotator cuff injuries. A multimodal approach combining rehabilitation, symptom control, and appropriate patient monitoring may improve pain and functional outcomes while potentially reducing the need for surgical intervention.

Introduction

Rotator cuff injuries are one of the most common causes of shoulder pain in all age groups. The degree of injuries affecting the rotator cuff varies from mild conditions, like acute reversible tendinitis, to more severe issues such as massive tears.[1] Rotator cuff tears can be evaluated radiographically based on factors like the size of the tear, the number of tendons involved, and the degree of retraction and atrophy. Since 1990, the Hamada classification has been widely used for the radiographic classification of massive rotator cuff tears.[2,3] Depending on the severity, it can affect the patient's functional activities and quality of life. When choosing a therapy, it's crucial to consider various factors impacting therapeutic outcomes, such as the duration of symptoms, the type of tear, the patient's age, any comorbidities, and their activity level.[4] Conservative management is usually the first option in treating rotator cuff tears until conservative management is considered unsuccessful and surgical management is chosen.

https://doi.org/10.31282/joti.v7n3.136

Other indications for surgical management of rotator cuff tears, aside from the failure of conservative management, remain controversial.

Conservative Management for Rotator Cuff Tears

Conservative management for rotator cuff tears itself consists of non-pharmacological and pharmacological therapies. Non-pharmacological therapy consists of physical therapy and surveillance, while pharmacological treatment consists of administering non-steroidal anti-inflammatory drugs (NSAIDs) and steroid injections. As a first-line treatment, conservative management can also affect the clinical outcome of postoperative patients. Certain therapies administered before surgery can yield positive effects. In contrast, others might negatively impact postoperative clinical outcomes, potentially leading to the progression of a partial-thickness tear into a full-thickness tear.[5,6] A study identified several factors that are correlated with a successful outcome following conservative treatment, such as preserved range of motion in external rotation, absence of impingement signs, minimal or no atrophy of the supraspinatus muscle, and preserved intramuscular tendon of the supraspinatus.[7] Understanding the effect and mechanism of action of existing conservative management can prevent patients from experiencing recurrence and complications from rotator cuff tears.

Physical Therapy

Physical therapy is the mainstay of conservative management of rotator cuff tears, focusing on preventive measures and restoring rotator cuff function. Prevention is being carried out by modifying activities, namely avoiding excessive activity on the shoulder joint, particularly the repetitive overhead movements. Modifying activities can prevent additional rotator cuff injuries or tears, potentially avoiding the need for surgery. In addition to preventive measures, focusing on recovering rotator cuff function is essential. The program of rotator cuff recovery is carried out on the principles of (1) stretching the anterior and posterior shoulder joint capsules, (2) exercises using elastic bands and light weights, and (3) plyometric shoulder exercises. Shoulder joint capsule stretching aims to restore the mobility of the shoulder joint to that of the healthy contralateral shoulder. Exercises using elastic bands and light weights aim to restore the strength and endurance of the muscles involved in moving and stabilizing the shoulder joint. Shoulder plyometric aims to restore proprioception and coordination of the shoulder joint.[8]

Patients with rotator cuff tears who underwent physical therapy experienced significant improvements in shoulder joint pain and function if compared to patients who did not undergo physical therapy.[9] Valencia et al. showed that preoperative physical therapy does not contribute to the postoperative recovery process.[10] In contrast, a recent randomized controlled study showed that preoperative physical therapy could positively affect postoperative recovery from pain, joint movement, and quality of life.[11] A multicenter prospective cohort study by Kuhn et al. shows that the success rate of physical therapy programs with or without an intraarticular injection is 90% at six weeks and 80% at two years.[12]

Surveillance

Surveillance aims to determine the progress of rotator cuff damage and is carried out by performing a physical examination and imaging of the shoulder joint every 6-12 months. The examination can also be done earlier or frequently if a patient with no symptoms suddenly experiences pain and a significant decrease in shoulder function. Physical examination was performed to assess the strength and movement of the shoulder joint. Imaging techniques such as MRI or ultrasound can be utilized to visualize the size of the tear. A significant increase in the size of the rotator cuff tear or decreased shoulder function is an indication of surgery. Effective surveillance measures can help prevent muscle atrophy and tendon retraction, reducing the risk of intraoperative complications.[5]

Oral Analgesics

The chief complaint of patients with rotator cuff tears is pain. Hence, pain management remains the key element of conservative treatment.[13] Ruthia et al. showed that oral analgesics combined with physical therapy relieve pain in as many as 50-90% of rotator cuff tear cases.[14] The available analgesic options include NSAIDs, paracetamol, and opioids. NSAIDs work by inhibiting cyclooxygenase (COX), which inhibits the production of prostaglandins and reduces inflammatory reactions such as pain. However, decreased plasma levels of prostaglandins can delay tendon-to-bone recovery and impede recovery of rotator cuff tears. In addition, NSAIDs can cause side effects on the cardiovascular, cerebrovascular, and gastrointestinal systems.[14]

The use of paracetamol can also be a therapeutic option. It can even be used as a first-line analgesic because it does not interfere with the tendon-to-bone recovery process. Paracetamol induces analgesia by minimally inhibiting COX and directly affecting the brain and spinal cord to impede the transmission of nociceptive stimuli.[15] With this property, paracetamol has milder side effects compared to NSAIDs. The use of oral opioids as analgesics in rotator cuff tears is not recommended due to the risk of opioid abuse.[16] Chronic use of preoperative opioids can also give a poor prognosis on the functional score, shoulder range of motion (ROM), shoulder strength, and visual analog scale compared with non-opioid analgesic users after arthroplasty.[17]

Subacromial Injections

Various regimens injected into the subacromial space are thought to alleviate shoulder pain caused by rotator cuff

tears. These include corticosteroid injections, platelet-rich plasma therapy, dextrose prolotherapy, and local anesthetic injections.

Subacromial bursa steroid injection is a common intervention for the treatment of shoulder pain.[18] Steroid injections can control pain in a relatively short time and are often used as an initial aid in rotator cuff tear patients with severe pain. However, there is a debate on whether corticosteroid injections are more beneficial compared to NSAIDs alone.[19,20] A study found that subacromial corticosteroids appear to have an additional benefit when used with NSAIDs and exercise regimens in the acute or subacute phase.[21] Although long-term steroid injections can cause a decrease in tendon durability, inhibit collagen healing, increase collagen necrosis, and inhibit the proliferation of fibroblasts. It can lead to recurrent tears in postoperative patients, increasing the risk of revision surgery.[22,23] Long-term subacromial steroid injections are not recommended unless the patient is not able to undergo surgery or in cases of chronic rotator cuff tears.[5] A study also found that patients will have a higher hazard ratio (HR) of 7.44 to develop RCT after steroid injections for a shoulder condition within a mean duration of 39 months.[24]

Platelet-rich plasma is a natural concentration of growth factors, and secretory proteins have shown an essential role in the healing of damaged tissue.[25-27] Injection to the subacromial bursa can decrease pain and improve patients' outcomes.[28] A double-blinded randomized control trial showed that platelet-rich plasma injection improved pain and function at three three-month follow-ups. However, a sustained benefit at 12 months of follow-up was not found.[29] Rossi et al. evaluated 150 patients who underwent platelet-rich plasma injections. The result showed a significant improvement in shoulder function, pain, and sleep disturbances that were maintained at the 12-month follow-up, and most patients returned to the same level of the sport before the injury.[30,31] Although platelet-rich plasma has been gaining interest because of its abundance of growth factors and ease of performing procedures, there is a lack of standardized protocols for platelet-rich plasma preparation and clinical applications.[32]

Prolotherapy with hyperosmolar dextrose solution is a potentially effective adjuvant to physical therapy for patients with rotator cuff tendinopathy. Since the 1950s, Prolotherapy has been used to treat ligament laxity and related musculoskeletal conditions due to its ability to stimulate healing.[33,34] Lately, prolotherapy has been used to treat chronic pain of musculoskeletal disorders such as chronic groin pain and chronic lower back pain.[35,36] Further studies need to be done to better understand the subpopulation with rotator cuff tendinopathy that benefits from prolotherapy, as well as to optimize the technique, including the number and period of repeat injections, volume and concentration of dextrose solution, and location of injection.[37]

Subacromial local anesthetic injections, such as lidocaine injections, can improve patients' comfort. A study that evaluated 40 subjects showed a significant improvement in patient comfort, which resulted in an increased range of motion, strength, and Constant-Murley score compared to the group injected with a placebo.[38,39]

Other Therapies

Other therapeutic modalities for rotator cuff tears include topical agents, massage, acupuncture, shock-wave therapy, and viscosupplementation.[5] Topical agents such as glyceryl trinitrate patches are more effective than placebo for rotator cuff disease among patients with short-term symptoms. Still, there needs to be more sufficient evidence regarding this statement.[40] The safety of acupuncture remains unknown due to a lack of research regarding acupuncture for patients with rotator cuff diseases.[41] Extracorporeal shock wave therapy (ESWT) gives therapy by sending shock waves through positioning and movement of the treatment probe, which is then transmitted to the pain point and produces mechanical stress and biological effects, thus promoting blood and lymphatic return, increasing metabolism, and blocking pain. ESWT is a non-invasive, easy-to-perform, cost-effective treatment.[42-45]

Surgical Indications for Rotator Cuff Tears

In addition to the failure of conservative management, other indications for operative treatment of rotator cuff tears are still controversial in various studies. In some cases, surgical management can be done immediately without prior conservative management, such as in full-thickness tears that occur acutely in healthy young individuals. In addition, an acute-on-chronic tear, when the patient suddenly loses the ability to abduct or flex the shoulder, is also an indication for surgery because this condition indicates a significant progression from a partial-thickness tear to a full-thickness tear.[46] A study demonstrated that early operative intervention (within less than three weeks) in acute traumatic full-thickness tear resulted in better improvement in active abduction motion and total active abduction compared to later surgical intervention.[47] Therefore, a systematic review suggests early surgical intervention should be performed on active people to restore their rotator cuff strength and motion.[48] A complete understanding of how the conservative treatment works, its effect, and the success rate of conservative therapy can help clinicians counsel the right time to move to surgical management in dealing with patients with rotator cuff tears.

Factors generally believed to affect the outcome and thus become indications to perform elective rotator cuff surgeries, including tear size, duration of symptoms, failure of nonoperative treatment, nocturnal pain, history of trauma, and limitations of activities of daily living.[48] According to Marx et al. although full-thickness rotator cuff tears are common, there is no definitive consensus regarding the

criteria for rotator cuff surgery. After reviewing approximately 86 papers meeting the study criteria, it was concluded that limitations in daily living activities, nonoperative treatment failure, a history of nocturnal pain, and the duration of nonoperative therapy could be considered as surgical indications for rotator cuff tears.[49] Many recommendations are available regarding the timing of surgical intervention on persistent symptoms cases after conservative measures have been done. Yet, only limited evidence-based data support those recommendations. Consequently, the timing of surgery is mainly determined by clinicians' preferences.

Conclusion

Rotator cuff tears can be challenging to manage, and identifying the appropriate treatment can be complex. However, it is essential to note that therapy can significantly determine the optimal time for surgical management. By collaborating with a skilled clinician, individuals with rotator cuff tears can gain valuable insights into their condition, allowing them to make informed decisions regarding their treatment options. Therefore, it is recommended that patients consider scheduling a therapy session, as it can be a crucial step toward achieving a successful recovery.

Conflict of interest: All authors declare that they have no conflicts of interest

References

1. Clark JM, Harryman DT 2nd. Tendons, ligaments, and capsule of the rotator cuff. Gross and microscopic anatomy. The Journal of Bone & Joint Surgery. 1992;74(5):713-25. PMID: 1624486.
2. Hamada K, Yamanaka K, Uchiyama Y, Mikasa T, Mikasa M. A radiographic classification of massive rotator cuff tear arthritis. Clinical Orthopaedics and Related Research®. 2011 Sep;469:2452-60.
3. Hamada K, Fukuda H, Mikasa M, Kobayashi Y. Roentgenographic findings in massive rotator cuff tears a long-term observation. Clinical Orthopaedics and Related Research®. 1990 May 1;254:92-6.
4. Oh LS, Wolf BR, Hall MP, Levy BA, Marx RG. Indications for rotator cuff repair. Clinical Orthopaedics and Related Research. 2007;455:52–63
5. McGrath T. Management of rotator cuff tears. Waltham, MA: UpToDate. 2022.
6. Longo UG, Risi Ambrogioni L, Candela V, Berton A, Carnevale A, Schena E, et al. Conservative versus surgical management for patients with rotator cuff tears: A systematic review and meta-analysis. BMC Musculoskeletal Disorders. 2021;22(1).
7. Tanaka, M., Itoi, E., Sato, K., Hamada, J., Hitachi, S., Tojo, Y., Honda, M., & Tabata, S. (2010). Factors related to the successful outcome of conservative treatment for rotator cuff tears. Upsala Journal of Medical Sciences
8. Matava MJ, Purcell DB, Rudzki JR. Partial-thickness rotator cuff tears. The American Journal of Sports Medicine. 2005;33(9):1405–17.
9. Dickinson RN, Ayers GD, Archer KR, Fan R, Page C, Higgins LD, et al. Physical therapy versus natural history in outcomes of rotator cuff tears: The rotator cuff outcomes workgroup (ROW) cohort study. Journal of Shoulder and Elbow Surgery. 2019;28(5):833–8.
10. Valencia C, Coronado R, Simon C, Wright T, Moser M, Farmer K, et al. Preoperative physical therapy treatment did not influence postoperative pain and disability outcomes in patients undergoing shoulder arthroscopy: A prospective study. Journal of Pain Research. 2016;Volume 9:493–502.
11. Almeida LL, Mendes Júnior AF, Neto Jda, Simoni LF, Lopes KH, Guimarães PC, et al. Pre-operative scapular rehabilitation for arthroscopic repair of traumatic rotator cuff tear: Results of a randomized clinical trial. International Journal of Sports Physical Therapy. 2021;16(1).
12. Kuhn, J. E., Dunn, W. R., Sanders, R., An, Q., Baumgarten, K. M., Bishop, J. Y., Brophy, R. H., Carey, J. L., Holloway, B. G., Jones, G. L., Ma, C. B., Marx, R. G., McCarty, E. C., Poddar, S. K., Smith, M. v., Spencer, E. E., Vidal, A. F., Wolf, B. R., & Wright, R. W. (2013). Effectiveness of physical therapy in treating atraumatic full-thickness rotator cuff tears: A multicenter prospective cohort study. Journal of Shoulder and Elbow Surgery.
13. Itoi, E. (2013). Rotator cuff tear: Physical examination and conservative treatment. Journal of Orthopaedic Science.
14. AlRuthia Y, Alghadeer S, Balkhi B, Almalag HM, Alsobayel H, Alodaibi F, et al. Efficacy of acetaminophen versus ibuprofen for the management of rotator cuff-related shoulder pain: Randomized open-label study. Saudi Pharmaceutical Journal. 2019;27(6):882–8.
15. Ohashi N, Kohno T. Analgesic effect of acetaminophen: A review of known and novel mechanisms of action. Frontiers in Pharmacology. 2020;11.
16. Gorbaty J, Odum SM, Wally MK, Seymour RB, Hamid N, Hsu JR, et al. Prevalence of prescription opioids for nonoperative treatment of rotator cuff disease is high. Arthroscopy, Sports Medicine, and Rehabilitation. 2021;3(2).
17. Thompson KM, Hallock JD, Smith RA, Brolin TJ, Azar FM, Throckmorton TW. Preoperative narcotic use and inferior outcomes after anatomic total shoulder arthroplasty. Journal of the American Academy of Orthopaedic Surgeons. 2019;27(5):177–82.
18. Lin, J., Weintraub, N., & Aragaki, D. (2008). Nonsurgical Treatment for Rotator Cuff Injury in the Elderly. Journal of the American Medical Directors Association, 9(9), 626–632. doi:10.1016/j.jamda.2008.05.003
19. Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: A meta-analysis. Br J Gen Pract 2005;55:224 –228.
20. Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. Cochrane Database Syst

Rev 2003;(1):CD004016.
21. Akgun K, Birtane M, Akarirmak U. Is local subacromial corticosteroid injection beneficial in subacromial impingement syndrome? Clin Rheumatol 2004;23:496–500.
22. Puzzitiello RN, Patel BH, Nwachukwu BU, Allen AA, Forsythe B, Salzler MJ. Adverse impact of corticosteroid injection on rotator cuff tendon health and repair: a systematic review. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2020 May 1;36(5):1468-75.
23. Baverel L, Boutsiadis A, Reynolds RJ, Saffarini M, Barthélémy R, Barth J. Do corticosteroid injections compromise rotator cuff tendon healing after arthroscopic repair?. JSES Open Access. 2018 Mar 1;2(1):54-9.
24. Lin C-Y, Huang S-C, Tzou S-J, Yin C-H, Chen J-S, Chen Y-S, et al. A positive correlation between steroid injections and cuff tendon tears: A cohort study using a clinical database. International Journal of Environmental Research and Public Health. 2022;19(8):4520.
25. Kon E, Filardo G, Delcogliano M, Presti ML, Russo A, Bondi A, Di Martino A, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma: new clinical application: a pilot study for treatment of jumper's knee. Injury. 2009 Jun 1;40(6):598-603.
26. Dhurat R, Sukesh M. Principles and methods of preparation of platelet-rich plasma: a review and author's perspective. Journal of cutaneous and aesthetic surgery. 2014 Oct;7(4):189.
27. Arnoczky SP, Shebani-Rad S. The basic science of platelet-rich plasma (PRP): what clinicians need to know. Sports medicine and arthroscopy review. 2013 Dec 1;21(4):180-5.
28. Rossi LA, Piuzzi N, Giunta D, Tanoira I, Brandariz R, Pasqualini I, Ranalletta M. Subacromial platelet-rich plasma injections decrease pain and improve functional outcomes in patients with refractory rotator cuff tendinopathy. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2021 Sep 1;37(9):2745-53.
29. Kwong CA, Woodmass JM, Gusnowski EM, Bois AJ, Leblanc J, More KD, Lo IK. Platelet-rich plasma in patients with partial-thickness rotator cuff tears or tendinopathy leads to significantly improved short-term pain relief and function compared with corticosteroid injection: a double-blind randomized controlled trial. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2021 Feb 1;37(2):510-7.
30. Rossi LA, Molina Rómoli AR, Bertona Altieri BA, Burgos Flor JA, Scordo WE, Elizondo CM. Does platelet-rich plasma decrease time to return to sports in acute muscle tear? A randomized controlled trial. Knee Surgery, Sports Traumatology, Arthroscopy. 2017 Oct;25:3319-25.
31. Rossi LA, Piuzzi N, Tanoira I, Brandariz R, Huespe I, Ranalletta M. Subacromial platelet-rich plasma injections produce significantly worse improvement in functional outcomes in patients with partial supraspinatus tears than in patients with isolated tendinopathy. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2023 Mar 29.
32. Sharma K, Das G, Sarvesh B, Agarwal A. Platelet-Rich Plasma for Degenerative Knee Joints: What is the Evidence?. Indian Journal of Pain. 2019 Sep 1;33(3):126-30.
33. Lin MT, Chiang CF, Wu CH, Huang YT, Tu YK, Wang TG. Comparative effectiveness of injection therapies in rotator cuff tendinopathy: a systematic review, pairwise and network meta-analysis of randomized controlled trials. Arch Phys Med Rehabil. 2018;100:336-349. e15. https://doi.org/10.1016/j.apmr.2018.06.028.
34. Reeves KD, Sit RWS, Rabago DP. Dextrose Prolotherapy: a narrative review of basic science, clinical research, and best treatment recommendations. Phys Med Rehabil Clin N Am. 2016;27:783-823
35. Topol GA, Reeves KD, Hassanein KM. Efficacy of dextrose prolotherapy in elite male kicking-sport athletes with chronic groin pain. Arch Phys Med Rehabil. 2005;86:697-702.
36. Maniquis-Smigel L, Reeves KD, Rosen HJ, et al. Short term analgesic effects of 5% dextrose epidural injections for chronic low Back pain: a randomized controlled trial. Anesthesiol. Pain Med. 2016;7:1-8.
37. Giovannetti de Sanctis E, Franceschetti E, De Dona F, Palumbo A, Paciotti M, Franceschi F. The efficacy of injections for partial rotator cuff tears: a systematic review. Journal of Clinical Medicine. 2020 Dec 25;10(1):51.
38. Forsythe B, Agarwalla A, Puzzitiello RN, Patel BH, Lu Y, Verma NN, Romeo AA, Cole BJ. Clinical function improves after Subacromial Injection of Local Anesthetic in full-thickness rotator cuff tears: a Randomized Control Trial. Orthopaedic journal of sports medicine. 2020 Jan 2;8(1):2325967119892331.
39. Constant CR, Murley AH. A clinical method of functional assessment of the shoulder. Clin Orthop Relat Res. 1987;214:160–164.
40. Cumpston, M., Johnston, R. V., Wengier, L., & Buchbinder, R. (2009). Topical glyceryl trinitrate for rotator cuff disease. Cochrane Database of Systematic Reviews.
41. Choi S, Lee J, Lee S, Yang GY, Kim KH. Acupuncture for Symptomatic Rotator Cuff Disease: A Systematic Review and Meta-analysis.
42. Moya D, Ramón S, Schaden W, et al. The role of extracorporeal shockwave treatment in musculoskeletal disorders. J Bone Joint Surg Am 2018;100:251–63
43. van der Worp H, van den Akker-Scheek I, van Schie H, et al. ESWT for tendinopathy: technology and clinical implications. Knee Surg Sports Traumatol Arthrosc 2013;21:1451–8.
44. Bosch G, Lin YL, van Schie HT, et al. The effect of extracorporeal shock wave therapy on the biochemical composition and metabolic activity of tenocytes in normal tendinous structures in ponies. Equine Vet J 2007; 39:226--231.

45. Feichtinger X, Monforte X, Keibl C, Hercher D, Schanda J, Teuschl AH, Muschitz C, Redl H, Fialka C, Mittermayr R. Substantial biomechanical improvement by extracorporeal shockwave therapy after surgical repair of rodent chronic rotator cuff tears. The American journal of sports medicine. 2019 Jul;47(9):2158-66.