



# Non-specific low back pain

Chris Maher, Martin Underwood, Rachelle Buchbinder

*Lancet* 2017; 389: 736–47

Published Online

October 10, 2016

[http://dx.doi.org/10.1016/S0140-6736\(16\)30970-9](http://dx.doi.org/10.1016/S0140-6736(16)30970-9)

Musculoskeletal Division, The George Institute for Global Health, Sydney Medical School, University of Sydney, Camperdown, NSW, Australia (Prof C Maher PhD); Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK (Prof M Underwood MD); and Monash Department of Clinical Epidemiology, Cabrini Hospital, and Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia (Prof R Buchbinder PhD)

Correspondence to: Prof Chris Maher, Musculoskeletal Division, The George Institute for Global Health, Sydney Medical School, University of Sydney, PO Box M201, Missenden Road, NSW 2050, Australia. [cmaher@georgeinstitute.org.au](mailto:cmaher@georgeinstitute.org.au)

Non-specific low back pain affects people of all ages and is a leading contributor to disease burden worldwide. Management guidelines endorse triage to identify the rare cases of low back pain that are caused by medically serious pathology, and so require diagnostic work-up or specialist referral, or both. Because non-specific low back pain does not have a known pathoanatomical cause, treatment focuses on reducing pain and its consequences. Management consists of education and reassurance, analgesic medicines, non-pharmacological therapies, and timely review. The clinical course of low back pain is often favourable, thus many patients require little if any formal medical care. Two treatment strategies are currently used, a stepped approach beginning with more simple care that is progressed if the patient does not respond, and the use of simple risk prediction methods to individualise the amount and type of care provided. The overuse of imaging, opioids, and surgery remains a widespread problem.

## Introduction

Low back pain is a symptom rather than a disease. Like other symptoms, such as headache and dizziness, it can have many causes. The most common form of low back pain is non-specific low back pain. This term is used when the pathoanatomical cause of the pain cannot be determined.

## Epidemiology, risk factors, and costs

In a 2008 review of the worldwide prevalence of low back pain, which included 165 studies from 54 countries, the mean point prevalence was estimated to be 18·3%, and 1-month prevalence 30·8%.<sup>1</sup> Low back pain was more common in female than male individuals and in those aged 40–69 years than in other age groups. Prevalence was greater in high-income countries (median 30·3% [IQR 16·9–46·6]) than middle-income (21·4% [10·6–38·6]) or low-income (18·2% [0·8–21·7]) countries, but there was no difference in prevalence between rural and urban areas. The study reported a positive correlation between a country's human development index and overall mean prevalence of low back pain ( $r=0\cdot088$ ;  $p<0\cdot001$ ).

Low back pain is the leading cause of years lived with disability in both developed and developing countries, and sixth in terms of overall disease burden (disability-adjusted life-years).<sup>2,3</sup> Many people with low back pain do not seek care; a review of ten population-based studies (13486 people) reported a pooled prevalence of care-seeking of 58% (95% CI 32–83).<sup>4</sup> Care-seeking is more common in women, and in individuals with previous low back pain, poor general health, and with more disabling or more painful episodes.<sup>4</sup>

The long-held belief that childhood low back pain is rare has been dispelled during the past decade. A study of 402406 adolescents from 28 countries found that 37·0% (95% CI 36·8–37·1) reported low back pain monthly or more frequently.<sup>5</sup> Low back pain was slightly more common in girls than boys (38·9% vs 35·0%). Prevalence increased with age, ranging from 27·4% (95% CI 27·2–27·7) in 11-year-olds, to 37·0% (36·7–37·2) in 13-year-olds, to 46·7% (46·5–47·0) in 15-year-olds. Across the 28 countries, prevalence ranged from around

28% (Poland, Lithuania, and Russia) to 51% (Czech Republic). Low back pain in childhood predicts low back pain in adult life. A study of 10000 Danish twins reported that those who had low back pain in adolescence were twice as likely to have it as adults (odds ratio [OR] 2·0 [95% CI 1·7–2·4]).<sup>6</sup>

We analysed data regarding risk factors for developing low back pain that were derived from systematic reviews of cohort studies. A review of lifting at work identified that both the weight of the load (OR 1·11 [95% CI 1·05–1·18] per 10 kg lifted) and the number of lifts (OR 1·09 [1·03–1·15] per ten lifts per day) increased risk.<sup>7</sup> In terms of lifestyle factors, smoking (OR 1·30 [1·16–1·45]),<sup>8</sup> obesity (OR 1·53 [1·22–1·92]),<sup>9</sup> and depressive symptoms (OR 1·59 [1·26–2·01])<sup>10</sup> all increased the risk of developing low back pain. These risk factors increased the odds of back pain by only a modest amount.

Comparison of estimates of the total, direct (health care), and indirect (lost production and lost household productivity) costs of low back pain between different countries is difficult. Even studies estimating costs for the same country and year come to widely different estimates—for example, two estimates of the indirect costs in the USA for 1996 were US\$18·5 billion and US\$28·2 billion.<sup>11</sup> Low back pain is a major contributor to health-care costs; typically, indirect costs are much higher than direct costs. An Australian estimate of the total cost in 2001 was AUS\$9 billion, with only

## Search strategy and selection criteria

We searched the Cochrane Library and PubMed for reports published in English from database inception until Feb 13, 2016, with the term “low back pain” and each heading in our Seminar (eg, “differential diagnosis”). Additionally, we identified current clinical guidelines, searched our existing records for relevant publications, and examined the reference lists of studies retrieved by the searches. We gave particular emphasis to clinical guidelines and systematic reviews over primary studies. Radicular pain (sciatica) is not discussed in this Seminar.

AUS\$1 billion of this amount accounted for by direct health-care costs.<sup>12</sup>

For the individual, low back pain can have profound economic effects. People with the disorder accumulate less wealth than those without the problem.<sup>13</sup> This effect increases with the addition of comorbidities.<sup>13</sup> Low back pain is the leading chronic health problem forcing older workers to retire prematurely, and forcing more people out of the workplace than heart disease, diabetes, hypertension, neoplasm, respiratory disease, and asthma combined.<sup>14</sup> Older people who retire early because of low back pain have substantially less total wealth and income-producing assets—about 87% less than those who remain in full-time employment.<sup>15</sup>

Several systematic syntheses of qualitative research describe the experience of living with low back pain. Froud and colleagues<sup>16</sup> (42 studies) suggest that patients' main concerns are the need to seek diagnosis, treatment, and cure as well as reassurance of the absence of pathological abnormality; concerns about regaining previous levels of health, physical and emotional stability, and engaging in meaningful activities; meeting social expectations and obligations; and wanting to be believed and have their experiences validated. MacNeela and co-workers<sup>17</sup> (38 studies) identified four themes: the undermining influence of pain, its disempowering impact, unsatisfying relationships with health-care professionals, and learning to live with the pain. Bunzli and colleagues<sup>18</sup> (18 studies) conceptualised the experience of low back pain as “suspended wellness”, “suspended self”, and “suspended future”. Snelgrove and colleagues<sup>19</sup> (28 studies) identified the effect on oneself, relationships with others (family and friends, health professionals, and organisation of care), and coping strategies as important themes.

### Clinical presentation, signs, and symptoms

In a study of 1172 consecutive patients with acute low back pain attending Australian primary care (family doctor, physiotherapist, or chiropractor), most (76%) reported having a previous episode.<sup>20</sup> Most patients had moderate to very severe pain intensity (80%) that caused moderate to extreme interference with daily function (76%). Patients reported problems being able to cope with their pain and were worried about the risk of persistence. A third (36%) were already taking medication for the disorder. Although most patients were working before the episode (76%), claims for compensation were uncommon (14%).

Acute low back pain can be triggered by physical factors (eg, lifting awkwardly) or psychosocial factors (eg, being fatigued or tired), or by a combination of the two (eg, being distracted while lifting).<sup>21</sup> However, about a third of patients with an acute episode cannot recall a trigger.<sup>22</sup> New episodes are more likely to begin early in the morning.<sup>21</sup> The weather does not affect low back pain, neither increasing the risk of a new episode<sup>23</sup> nor

worsening established episodes.<sup>24</sup> Findings from a US study of 1·82 million emergency department presentations for low back pain showed that 81% of episodes began at home, with lifting the most commonly cited cause.<sup>25</sup> Ethnic origin strongly determined incidence (presentations per 1000 person-years: 2·10 in Native Americans, 1·38 in African-Americans, 1·23 in white people, 0·40 in Hispanic people, and 0·20 in east Asians). The peak incidence rates were for people in their late 20s and those in their late 90s. By contrast, in Scottish general practice, consultations are much more common in middle age than early adulthood, with a further slight increase in old age ( $\geq 75$  years).<sup>26</sup> At all ages, female individuals consult more frequently than male individuals. Older people have greater physical disability as a consequence of their low back pain than have younger people.<sup>27</sup>

### Differential diagnosis

Low back pain is a symptom that accompanies several diseases. The diagnosis of non-specific low back pain implies no known pathoanatomical cause. Triage aims to exclude those cases in which the pain arises from either problems beyond the lumbar spine (eg, leaking aortic aneurysm); specific disorders affecting the lumbar spine (eg, epidural abscess, compression fracture, spondyloarthropathy, malignancy, cauda equina syndrome); or radicular pain, radiculopathy, or spinal canal stenosis. Remaining cases are non-specific low back pain. Several lumbar structures are plausible sources of pain (eg, the intervertebral disc, the facet joints), but clinical tests do not reliably attribute the pain to those structures.<sup>28</sup>

Most low back pain is non-specific (commonly cited as 90%).<sup>29</sup> Deyo and Weinstein<sup>30</sup> estimated that of patients with low back pain in primary care, about 4% would have a compression fracture, 3% would have spinal stenosis, 2% would have visceral disease, 0·7% a tumour or metastasis, and 0·01% an infection. In the previously mentioned Australian study (1172 patients with acute low back pain in primary care), fewer than 1% of patients had specific causes for their pain.<sup>31</sup> Only 11 cases of serious disease were identified: eight patients with osteoporotic fractures, two with inflammatory arthritis, and one with cauda equina syndrome. A Dutch primary care study of 669 people (aged  $> 55$  years) with back pain identified 33 cases of fracture and four cases of spinal malignancy.<sup>32</sup> Once osteoporotic fractures, which largely affect older people, are excluded, specific causes of low back pain are very uncommon in primary care, but are more common in secondary and tertiary settings. In a Cochrane diagnostic review (14 studies), the median prevalence of fracture in patients presenting with low back pain was 3·6% in primary care and 6·5% in secondary and tertiary care.<sup>33</sup>

Red flags (eg, night pain, unexplained weight loss) have been promoted to identify patients who require

further diagnostic work-up for serious disorders. There are many possible red flags. Although these are worthy of elicitation as part of the clinical assessment, taken alone few have useful diagnostic accuracy. A Cochrane review concluded that only one of 24 red flags for malignancy had acceptable diagnostic accuracy.<sup>34</sup> The problems with false positives are well illustrated in an Australian study, in which 80% of patients with acute low back pain had at least one red flag present, yet fewer than 1% had a medically serious disease.<sup>31</sup> Part of the problem is considering a single clinical feature in isolation. A more useful approach is to rely on a combination of clinical features to identify individuals who require further diagnostic work-up.<sup>35</sup>

### Diagnostic investigations

Diagnostic investigations have no role in the management of non-specific low back pain. Although diagnoses based on lumbar structures (discogenic low back pain, facet joint pain, sacroiliac joint pain) remain popular in some settings, the available clinical tests for these conditions have insufficient accuracy.<sup>28</sup>

Diagnostic investigations have a role when the clinician suspects a specific disease process that would be managed differently from non-specific low back pain. The threshold for triggering investigations should reflect both the consequence of missing or delaying the diagnosis and the clinician's assessment of the likelihood of a more serious disease being present. The American College of Physicians' guideline for diagnostic imaging suggests immediate imaging when there are major risk

factors for cancer, risk factors for spinal infection or cauda equina syndrome, or severe neurological deficits.<sup>36</sup> By contrast, these guidelines advise deferral of imaging pending a trial of therapy when there are weaker risk factors for cancer or risk factors for spondyloarthritis, vertebral compression fracture, radiculopathy, or spinal stenosis (table 1).

Findings from a systematic review (12 studies) did not show consistent associations between MRI findings and future episodes of low back pain.<sup>46</sup> Although guidelines discourage routine imaging for non-specific low back pain,<sup>47</sup> this approach remains common. In Australian<sup>48</sup> and US primary care,<sup>49</sup> about a quarter of patients presenting with a new episode of low back pain undergo imaging. In a US emergency department setting, a third of patients received imaging,<sup>50</sup> compared with more than a half of patients in an Italian emergency department.<sup>51</sup> Attempts to establish what proportion of imaging procedures were not indicated range from 54% for a US health insurer,<sup>52</sup> to 47% at four Iranian radiology clinics,<sup>53</sup> to 31% in the US Veterans Health Administration.<sup>54</sup> Both patients<sup>55,56</sup> and clinicians<sup>57,58</sup> erroneous beliefs that imaging is essential in the management of low back pain are potential drivers of unnecessary imaging.

Indiscriminate imaging is costly (and time-consuming), can cause unnecessary exposure to radiation, and might be harmful. A systematic review<sup>39</sup> of six randomised controlled trials established that imaging does not improve clinical outcomes. Observational studies have linked liberal imaging with greater work absence, and greater use of other health services including injections

Alerting clinical features		Initial diagnostic work-up
Cancer	NICE guidance advises investigation for myeloma in people aged 60 years or older with persistent bone pain (particularly back pain) or unexplained fracture and investigation for pancreatic cancer in people aged 60 years or older with back pain and weight loss. <sup>41</sup> The most common causes of bony metastases are breast, lung, and prostate cancer. Together, these cancers account for 68% of bony metastases, <sup>42</sup> including spine. Other tumours, including renal and gastric cancer, can also metastasise to the spine and spinal metastases can be the first presentation of cancer. We were unable to find good epidemiological data for the incidence of new-onset spinal metastases after apparently successful treatment for cancer	For strong suspicion of cancer: FBC, ESR, CRP; MRI <sup>43</sup> For lower suspicion of cancer defer work-up until a trial of therapy has been completed
Vertebral infection	New onset of low back pain with fever and history of intravenous drug use or recent infection, immunosuppression, recent spinal procedure or fever/chills in addition to pain with rest or at night. Consider spinal tuberculosis in endemic areas or in migrants from these areas	FBC, ESR, CRP; MRI <sup>43</sup> Urgent referral for specialist care
Cauda equina syndrome	New bowel or bladder dysfunction, saddle anaesthesia, persistent or increasing lower motor neuron weakness	MRI and CT Urgent referral to spine surgeon
Vertebral compression fracture	History of osteoporosis, use of glucocorticoids, significant trauma, or older age (>65 years for women or >75 years for men)	Radiography (if negative result and there is continuing clinical suspicion consider MRI) <sup>43</sup>
Axial spondyloarthritis	Consider axial spondyloarthritis in patients with chronic back pain (duration ≥3 months) with back pain onset before 45 years of age if one or more of the following are present: (1) inflammatory back pain*; (2) peripheral manifestations (in particular arthritis, enthesitis, and/or dactylitis); (3) extra-articular manifestation (psoriasis, inflammatory bowel disease, and/or uveitis); (4) positive family history of spondyloarthritis; and (5) good response to non-steroidal anti-inflammatory drugs	For strong suspicion of axial spondyloarthritis refer to a rheumatologist. If unsure, defer work-up until a trial of therapy has been completed. If no response, and suspicion remains, refer to a rheumatologist
Radicular pain or radiculopathy (previously called sciatica)	Back pain with leg pain in an L4, L5, or S1 nerve root distribution, positive result on straight leg raise or crossed straight leg raise test. The sensitivity and specificity of these tests is mixed. <sup>44</sup> Sensory loss, weakness, or reduced reflex (ie, evidence of radiculopathy)	Defer work-up until a trial of therapy has been completed; consider MRI in patients who are candidates for surgery
Spinal canal stenosis	Bilateral buttock, thigh, or leg pain; older age; pseudoclaudication	Defer work-up until a trial of therapy has been completed; consider MRI in patients who are candidates for surgery

NICE=National Institute for Health and Care Excellence. FBC=full blood count. ESR=erythrocyte sedimentation rate. CRP=C-reactive protein. \*At least four of (1) age at onset 40 years or younger; (2) insidious onset; (3) improvement with exercise; (4) no improvement with rest; and (5) pain at night (with improvement upon getting up).<sup>45</sup>

**Table 1: Identification of specific disorders that can present as low back pain<sup>37-40</sup>**

and surgery.<sup>59,60</sup> Imaging can detect incidental findings that could be viewed by a clinician as targets for therapy or a cause for concern by the patient. For example, a review of 33 studies (3310 patients) reported that the prevalence of disc bulge in asymptomatic people was 30% in 20-year-olds, 60% in 50-year-olds, and increased to 84% in 80-year-olds.<sup>61</sup>

## Prevention

There are popular interventions to prevent low back pain that are based around limiting exposure to risk factors. Examples of interventions that aim to reduce excessive loading of the spine include use of lifting devices in workplaces, braces to support the spine, and ergonomic office furniture. Few trials have investigated such strategies; most prevention interventions have only face validity.

A 2016 review (21 studies, 30850 patients) concluded that exercise alone or in combination with education is effective for preventing low back pain, whereas other interventions, including education alone, back belts, and shoe insoles, do not seem to prevent low back pain.<sup>62</sup> Although some caution is required because the trials are typically quite small, the size of the protective effect for interventions found effective was large. For example, exercise and education reduced the risk of an episode of low back pain in the next year by 45%, whereas exercise alone reduced the risk by 35%. The programmes did not just focus on back-specific exercises, but also included exercises for the upper and lower limbs plus exercises to improve aerobic fitness, strength, flexibility, and skill or coordination. The exercise programmes required a substantial commitment in time from participants. For example, the exercise programme investigated by Soukup and colleagues<sup>63</sup> required participants to complete 20 group sessions of exercises and education over 13 weeks.

## Clinical course

The clinical courses of acute and persistent low back pain are typically presented as being completely different. A common view is that most cases of acute low back pain recover completely within 4–6 weeks but persistent low back pain has a very poor prognosis with recovery unlikely. This simple portrayal of the course of low back pain needs reconsideration.

A systematic review (24 studies, 4994 patients) summarised the clinical course of low back pain with pooled mean pain scores expressed on a 0 (no pain) to 100 (worst possible pain) scale.<sup>64</sup> For 15 cohorts with acute pain, the pooled mean pain score was 52 (95% CI 48–57) at baseline, 23 (21–25) at 6 weeks, 12 (9–15) at 26 weeks, and six (3–10) at 52 weeks, whereas for six cohorts with persistent pain the pooled mean pain score was 51 (44–59), 33 (29–38), 26 (20–33), and 23 (16–30) at the same timepoints. A study of patients presenting to primary care clinics in Sydney, Australia, reported that

72% of patients with acute low back pain had completely recovered by 12 months,<sup>65</sup> whereas 42% of those with persistent low back pain<sup>66</sup> recovered within 12 months. Of those presenting with acute pain who recovered, 33% (95% CI 28–38) had a recurrence within the next 12 months.<sup>67</sup> This pattern of results suggests that we might have overestimated the good prognosis for patients with acute low back pain and underestimated the potential for improvement in people with persistent low back pain.

Another view of the course of low back pain comes from studies that characterised the prognoses of individual patients by studying their trajectories of pain over time. A secondary analysis of the PACE trial<sup>34</sup> (1585 patients) identified five clusters of pain trajectories during a 12-week period for patients receiving first-line care for acute low back pain; 36% had rapid recovery, 34% improved more slowly but recovered by 12 weeks, 14% had incomplete recovery by 12 weeks, 11% had fluctuating pain, and 5% had persistent high pain during the 12-week period.

A range of biological, psychological, societal, and work factors are linked to poor outcomes. A review of 17 systematic reviews of the prognosis of low back pain (162 primary studies) reported that the following factors were consistently associated with poor outcome: higher disability, presence of sciatica, older age, poor general health, increased psychological or psychosocial distress, negative cognitive characteristics, poor relationships with colleagues, heavy physical work demands, and presence of compensation.<sup>68</sup>

## Acute management

Table 2 summarises the evidence from systematic reviews about the effects of treatments for acute low back pain on short-term pain outcomes. When possible, we relied on Cochrane reviews. By definition, non-specific low back pain does not have a known pathoanatomical cause. There are, therefore, no specific treatments that can be provided for non-specific low back pain. Instead, management focuses on reducing pain and its consequences, including any associated disability. Although there are some slight differences between clinical practice guidelines from various countries,<sup>47</sup> the advice for management is quite similar. The main components of management consist of education and reassurance, analgesic medicines, non-pharmacological therapies, and timely review based on individual patient needs, likely prognosis, treatment prescribed, and remaining concerns about serious pathological abnormality.

Following clinical assessment, the clinician should explain to the patient that a medically serious cause for his or her low back pain is highly unlikely, and there is no current need for any tests or imaging. This discussion is important because many patients expect imaging to be done and some also worry that their low back pain is a sign of something serious.<sup>55</sup> Patients can be provided with an explanation as to why imaging is unhelpful in

	Effect	Quality of evidence
<b>Education and reassurance</b>		
Bed rest vs staying active <sup>69</sup>	0.4 (−3.2 to 4.0)	Low
Heat vs sham <sup>70</sup>	−32.2 (−38.7 to −25.2)	Very low*
<b>Pharmacological therapies (vs placebo)</b>		
Paracetamol <sup>71</sup>	−0.5 (−2.9 to 1.9)	High
NSAIDs <sup>72</sup>	−8.4 (−12.7 to −4.1)	High*
Muscle relaxants <sup>73</sup>	−21.3 (−29.0 to −13.5)	High
Opioids <sup>74</sup>	No trials	Very low
<b>Non-pharmacological therapies</b>		
Manual therapy vs inert interventions <sup>75</sup>	−12.0 (−20.0 to −4.0)	Low
Manual therapy vs all other treatments <sup>75</sup>	−1.5 (−4.9 to 1.8)	Low
Massage vs inactive control <sup>76</sup>	−20.5 (−37.0 to −12.8)	Very low
Exercise vs no treatment, sham, or placebo <sup>77</sup>	0.6 (−11.5 to 12.7)	High*
Exercise vs other conservative treatment <sup>77</sup>	−0.3 (−5.1 to 4.2)	High*
Acupuncture vs placebo <sup>78</sup>	−10.6 (−25.3 to 4.1)	Moderate

Data taken from systematic reviews of randomised controlled trials. Treatment effects are weighted mean differences with 95% CI for 0–100 point pain scale at short-term follow-up. Negative effects represent greater pain reduction. Effects in standardised mean differences were transformed presuming an SD of 20. Quality of evidence is the GRADE rating on a scale from very low to high. NSAIDs=non-steroidal anti-inflammatory drugs. \*Our GRADE rating because none originally provided.

**Table 2: Effects of interventions for acute low back pain on short-term pain outcomes**

identifying the cause of non-specific low back pain (ie, degenerative changes are commonly present and increase with age irrespective of the presence of low back pain), and advised that it is unlikely to alter the immediate management of their problem. The next step is to educate the patient about the problem, its cause(s), and likely outcome, explain that little or no medical treatment is required for most patients, and outline what the patient can do to promote recovery. Identifying and addressing any misconceptions the patient might have,<sup>79,80</sup> either by providing the patient with the opportunity to ask questions or by probing questions, is important, because misconceptions about low back pain are quite common<sup>55,81</sup> and could adversely affect outcome. These misconceptions can include fear avoidance beliefs, which are more common in those who seek care,<sup>82</sup> and patient expectations of poor recovery.<sup>83</sup>

Patient education can be effective for outcomes such as return to work and global impression of recovery.<sup>84</sup> Although education might seem simple, many patients do not receive any education for their low back pain from their family doctor.<sup>48</sup> A systematic review (14 trials, 4872 participants) concluded that patient education in primary care does provide long-term reassurance—ie, reduces the fears and concerns of the patient and reduces subsequent primary care visits for low back pain.<sup>85</sup>

Notably, education was more effective when provided by a medical doctor than by a nurse or physiotherapist.<sup>85</sup>

Traditionally, bed rest was advised for low back pain. The contemporary view is that in most cases it should be avoided. The patient should remain as active as possible and either continue or gradually resume their normal activity levels, and if possible remain at work. The patient should also be encouraged to use simple self-care options to relieve pain such as use of a hot pack.<sup>70</sup>

Clinical practice guidelines traditionally endorsed the WHO analgesic ladder,<sup>47</sup> beginning with simpler options before moving to more powerful analgesics. However, paracetamol is ineffective for acute low back pain<sup>71</sup> and no trials have assessed the efficacy of opioids for acute pain.<sup>74,86</sup> Although there is evidence of effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs)<sup>87</sup> and muscle relaxants,<sup>73,87</sup> any potential benefits should be weighed against the risk of harm. A 2015 trial (323 patients) reported similar outcomes in patients receiving naproxen plus placebo, naproxen plus cyclobenzaprine (a muscle relaxant), or naproxen plus oxycodone and paracetamol.<sup>88</sup> Because of the paucity of evidence on opioid effectiveness, and concerns that the use of opioids for low back pain generates serious avoidable harms,<sup>89</sup> their use is questionable. However, surveys show that the use of opioids is high—eg, they are prescribed to 45% of patients presenting with low back pain at emergency departments in the USA.<sup>90</sup> The 2016 UK National Institute for Health and Care Excellence (NICE) draft guideline for management of low back pain<sup>91</sup> moves away from the traditional analgesic ladder and advises only two options: oral NSAIDs at the lowest effective dose for the shortest time possible and the use of a weak opioid (with or without paracetamol) if the patient does not tolerate or respond to an NSAID.

Non-pharmacological therapies for acute low back pain include treatments such as manual therapy, exercise, massage, and acupuncture. Guidelines vary in their recommendations for these therapies. One approach is to only consider these therapies for patients who do not respond to first-line care (education, reassurance, and analgesic medicines). The rationale for this approach is that the clinical course of acute pain when patients receive good-quality first-line care is favourable: about 50% of patients recover completely in 2–3 weeks.<sup>92</sup> Although not associated with substantial harms, providing non-pharmacological therapies to all patients is unnecessary and wasteful of health-care resources.

A recent development of this approach is to use brief risk prediction methods such as the short-form Örebro Musculoskeletal Pain Screening Questionnaire<sup>93</sup> and the Keele STarT Back Screening Tool<sup>94,95</sup> to identify patients with an increased likelihood of delayed recovery and to intervene with these patients from day one, rather than waiting for failure of first-line care. These methods can also help the clinician to better understand the reasons for a potentially poor prognosis and so target



interventions accordingly. For example, the short-form Örebro questionnaire includes ten items to assess pain, function, recovery expectations, psychological distress, and fear of pain or movement.

### Long-term management

No treatments can cure persistent low back pain, but interventions are available that reduce pain and disability, and address the consequences of long-term pain (table 3). Many patients and clinicians find this position hard to accept, which provides a fertile ground for people with vested interests to market non-evidence-based treatments that purport to cure persistent back pain. Part of the challenge of managing persistent low back pain is to guide patients away from the wide array of centres and therapists making false promises.

The effects of chronic pain on patients varies substantially, from those who experience minimal disruption to their life through to people who are severely disabled and for whom participation in work, social, and family roles is severely restricted. For some patients, dependence on prescribed medication, alcohol, or other drugs, and psychological distress complicate their presentation. When the effect of the pain becomes broader, and the health and social problems to be managed more complex, team-based care is usually required. By comparison with management of acute low back pain, the management of persistent low back pain has greater emphasis on non-pharmacological therapies and greater consideration of management of comorbidities such as depression.<sup>104</sup>

The messages for education and reassurance are much the same as for acute low back pain—ie, provide advice and information to explain the nature and likely course of low back pain, promote self-management, and encourage the patient to be as physically active as possible and remain at work. However, the evidence base for these guideline recommendations is quite limited.

The WHO pain ladder is, in our view, inappropriately proposed for persistent low back pain.<sup>40,105,106</sup> Systematic reviews support the effectiveness of NSAIDs<sup>96</sup> and opioids for patients with chronic low back pain,<sup>107</sup> but not paracetamol,<sup>71</sup> muscle relaxants,<sup>73</sup> tricyclic antidepressants,<sup>97</sup> or neuromodulators such as gabapentin or pregabalin.<sup>87,108</sup> The 2016 NICE draft guideline<sup>91</sup> completely dispenses with the notion of an analgesic ladder, and endorses use of oral NSAIDs only. The guideline explicitly advises against opioids for chronic low back pain, arguing that their effect on pain and function is too small to be clinically important. However, this advice seems inconsistent with the endorsement of other therapies with similarly small effect sizes, such as exercise and manual therapy.

A 2015 review of opioids for persistent low back pain provides some guidance for prescribing opioids to patients with this condition,<sup>89</sup> but the principles apply equally for any pain medicine used with patients with

	Effect	Quality of evidence
<b>Pharmacological therapies (vs placebo)</b>		
Paracetamol <sup>71</sup>	0.0 (−9.7 to 9.7)	Very low
NSAIDs <sup>96</sup>	−3.3 (−5.3 to −1.3)	Low
Skeletal muscle relaxants <sup>73</sup>	−4 (−8.6 to 0.6)	Very low
Tricyclic antidepressants <sup>97</sup>	−0.80 (−5.0 to 3.4)	High*
Benzodiazepines <sup>73</sup>	No trials	Very low
Opioids <sup>74</sup>	−8.6 (10.4 to −6.6)	Moderate
<b>Non-pharmacological therapies</b>		
Manual therapy vs ineffective, sham, or inert control <sup>98</sup>	−6.07 (−11.52 to −0.62)	Very low
Manual therapy vs effective interventions <sup>98</sup>	−3.04 (−5.98 to −0.10)	Very low
Massage vs inactive controls <sup>76†</sup>	−15.0 (−18.0 to −12.0)	Low
Massage vs active controls <sup>76†</sup>	−7.4 (−12.4 to 2.6)	Low
Exercise vs no treatment, sham, or placebo <sup>77</sup>	−8.58 (−18.46 to −1.29)	High*
Exercise vs other conservative treatment <sup>77</sup>	−4.47 (−7.41 to −1.53)	High*
Acupuncture vs placebo <sup>78</sup>	−11.1 (−23.3 to 1.1)	Moderate
Acupuncture vs no treatment <sup>78</sup>	−11.9 (−21.7 to −0.21)	Moderate
Ultrasound vs placebo <sup>99</sup>	−7.1 (−18.0 to 3.8)	Low
TENS vs placebo <sup>100</sup>	−2.3 (−9.6 to 5.0)	Moderate*
Cognitive behavioural therapy vs waiting list control <sup>101</sup>	−12.0 (−19.4 to −4.4)	Moderate*
Behavioural treatment vs usual care <sup>101</sup>	−5.18 (−9.79 to −0.57)	Moderate*
Behavioural treatment vs other treatments (exercise) <sup>101</sup>	−2.31 (−6.33 to 1.70)	Moderate*
Multidisciplinary treatment vs usual care <sup>102</sup>	−11.0 (−7.4 to −0.8)	Moderate
Multidisciplinary treatment vs physical treatments <sup>102</sup>	−6.0 (−10.8 to −1.2)	Moderate
Radiofrequency denervation facet joint vs placebo <sup>103‡</sup>	−14.7 (−22.8 to −6.7)	Low
Radiofrequency denervation disc vs placebo <sup>103</sup>	−4.1 (−15.4 to 7.2)	Low
Radiofrequency denervation SIJ vs placebo <sup>103</sup>	−21.2 (−54.5 to 12.1)	Low
Data taken from systematic reviews of randomised controlled trials. Treatment effects are weighted mean differences with 95% CI for 0–100 point pain scale at short-term follow-up; negative effects represent greater pain reduction. Effects in standardised mean differences were transformed presuming an SD of 20. Quality of evidence is the GRADE rating on a scale from very low to high. NSAIDs=non-steroidal anti-inflammatory drugs. TENS=transcutaneous electrical nerve stimulation. SIJ=sacroiliac joints. *Our GRADE rating because none originally provided. †The Cochrane review of massage merged subacute and persistent low back pain trials. <sup>76</sup> ‡Although the Cochrane review of radiofrequency denervation reported a short-term effect for facet joint pain, the investigators emphasised the lack of high-quality evidence. <sup>103</sup>		
<b>Table 3: Effects of interventions for persistent low back pain on short-term pain outcomes</b>		

persistent low back pain: (1) discuss harms and benefits with the patient; (2) keep the dose as low as possible and consider intermittent prescription; (3) begin with a short trial and discontinue if treatment goals are not met; and (4) use a pain contract to establish expectations. The 2016 US Centers for Disease Control and Prevention (CDC) guideline for prescribing opioids for chronic pain advises that “non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain” and that “if opioids are used, they should be combined with non-pharmacologic therapy and non-opioid pharmacologic therapy”.<sup>109</sup>

Leading authorities in the low back pain specialty have warned that opioids have been prescribed too freely for low back pain and with insufficient care.<sup>89</sup> A 2013 Cochrane review that assessed the efficacy of opioids in adults with chronic low back pain reported evidence of short-term effectiveness but identified no randomised

**Panel: Non-pharmacological interventions for persistent non-specific low back pain**

- Manual therapy includes high velocity thrust techniques (manipulation, adjustment) and lower velocity oscillatory techniques (mobilisation). A 2011 Cochrane review<sup>98</sup> reported effectiveness of manual therapy. The 2016 UK National Institute for Health and Care Excellence (NICE) draft guideline<sup>91</sup> for management of low back pain recommends manual therapy only when provided as part of a multimodal package.
- Massage has mixed support. Although it is endorsed in the guideline from the American College of Physicians and the American Pain Society (ACP/APS),<sup>40</sup> a 2015 Cochrane review update dismissed this therapy for chronic low back pain.<sup>76</sup> The 2016 NICE draft guideline<sup>91</sup> recommends massage only when provided as part of a multimodal package.
- Return to work programmes are endorsed in the 2016 NICE draft guideline.<sup>91</sup>
- Exercise includes approaches that follow exercise physiology principles, traditional mind-body exercises (eg, Tai Chi, yoga<sup>112</sup>), styles that emphasise precise control of movement and bodily awareness (eg, pilates,<sup>113</sup> motor control exercise,<sup>114</sup> Alexander technique<sup>115,116</sup>), and approaches that incorporate psychological principles (eg, graded exposure, graded activity<sup>117</sup>). A 2005 Cochrane review supports effectiveness.<sup>77</sup> The 2016 NICE draft guideline recommends group exercise,<sup>91</sup> but there is evidence that this format is less effective than individually supervised programmes.<sup>118</sup>
- Acupuncture has mixed support. Although a 2005 Cochrane review reported that acupuncture is effective in the short term,<sup>119</sup> and this conclusion was supported by a 2015 review,<sup>120</sup> the 2016 NICE draft guideline<sup>91</sup> reverses its earlier endorsement of this intervention in the 2009 guideline.<sup>105</sup>
- Cognitive behavioural therapy has evidence from a Cochrane review that it is effective in the short term.<sup>101</sup> The extended follow-up of the BEST trial<sup>121</sup> showed a long-term benefit. The 2016 NICE draft guideline advises that psychological therapies should only be used as part of multimodal treatment packages.<sup>91</sup>
- Multidisciplinary treatment is endorsed in the ACP/APS guideline<sup>40</sup> and the 2016 NICE draft guideline<sup>91</sup> (where it is called combined physical and psychological therapy). A 2014 Cochrane review<sup>102</sup> showed that the treatment is effective for reducing pain, disability, and improving work status.
- Injections are not a recommended treatment in either the ACP/APS guideline or the 2016 NICE draft guideline.<sup>40,91</sup>
- Radiofrequency neurotomy is endorsed for low back pain thought to arise from the facet joints in the 2016 NICE draft guideline,<sup>91</sup> but a 2015 Cochrane review<sup>103</sup> does not support this procedure for pain thought to arise from facet joint, disc, or sacroiliac joint on the grounds that high-quality evidence is absent (four very low quality trials, 160 patients). A 2016 Dutch trial<sup>122</sup> (251 patients) showed that the addition of radiofrequency neurotomy to an exercise programme was not effective or cost-effective for patients with low back pain thought to arise from the facet joints.
- Epidural steroid injections have a small short-term effect in people with radicular pain and no benefit for spinal stenosis,<sup>123</sup> but are not indicated for non-specific low back pain as indicated in the recommendations of the 2016 NICE draft guideline.<sup>91</sup>
- Prolotherapy (injection of irritating solutions into ligaments) has not proved effective.<sup>124</sup>
- Antibiotic prescription for low back pain accompanied by modic changes is controversial. This strategy has support from one trial,<sup>125</sup> but the trial and its rationale have been challenged.<sup>126</sup> The 2016 NICE draft guideline did not offer a recommendation for or against use of antibiotics in patients with low back pain.<sup>91</sup>
- Spinal cord stimulators or intrathecal pumps have not had their efficacy investigated.
- Referral for an opinion about surgery is often considered for those who do not respond to conservative care, but the logic of this approach is questionable because most surgical interventions used for chronic low back pain are either known to be ineffective or have not been clinically assessed. Spinal fusion is commonly used in patients with persistent low back pain but does not provide better outcomes than conservative care.<sup>127</sup> The 2016 NICE draft guideline advises against disc replacement and recommends spinal fusion only be done within a randomised controlled trial.<sup>91</sup>

controlled trials investigating long-term use.<sup>107,110</sup> This discrepancy is an important evidence gap because about half the people taking opioids long term have persistent low back pain.<sup>89</sup> Contrary to popular opinion, opioids have only modest effects on pain in patients with chronic low back pain and no benefit on function; furthermore, about 50% of patients do not tolerate the medicine.<sup>86</sup> Findings from observational studies<sup>89,110</sup> suggest that opioid analgesics are associated with harms such as overdose deaths and dependence, and increased risk for other health problems such as falls, fractures, depression, and sexual dysfunction.<sup>111</sup> With long-term use, there is

the potential for tolerance (the patient is less sensitive to opioids) and hyperalgesia (the patient becomes more sensitive to pain stimuli).<sup>89</sup>

Non-pharmacological treatments are emphasised over pharmacological interventions in the management of persistent non-specific low back pain. A broader range of non-pharmacological therapies are endorsed, but these vary by endorsing body. For example, the guideline from the American College of Physicians and the American Pain Society<sup>40</sup> endorses manual therapy, exercise therapy, massage, acupuncture, yoga, cognitive behavioural therapy, and intensive interdisciplinary treatment, whereas the 2016

NICE draft guideline<sup>91</sup> endorses self-management, exercise, manual therapy, psychological therapies, combined physical and psychological programmes, return-to-work programmes, and radiofrequency denervation. Several non-pharmacological therapies are not endorsed in the 2016 NICE draft guideline,<sup>91</sup> such as electrotherapies (eg, ultrasound and electrical stimulation), traction, belts or corsets, foot orthotics, and rocker sole shoes. A brief summary of the evidence for non-pharmacological interventions for persistent low back pain is provided in the panel and table 3.

### Controversies and uncertainties

Although low back pain occurs in both children and older people, we have a limited understanding of how to manage the problem in these groups because they are usually excluded from studies of interventions. A systematic review of the management of low back pain in children and adolescents identified only 15 trials,<sup>128</sup> but a search of CENTRAL on March 18, 2016, across all age groups, identified 5354 trials. Many trials exclude workers, people with comorbidities, individuals on compensation, or immigrants who do not speak the language of the country; this evidence gap is important because these patient groups tend to have a worse prognosis when they have low back pain.<sup>65</sup>

A belief that individualised treatment will yield better outcomes is widespread in the clinical back pain community.<sup>129</sup> Most of the studies that have claimed to provide evidence of treatment effect modification are flawed,<sup>130–132</sup> and the small number of robust studies either await replication or have not had their results replicated.<sup>133</sup> One of the challenges in this area is that claims of a subgroup effect are more credible if they have a biological rationale,<sup>134</sup> which is challenging for non-specific low back pain.

The use of injection and ablation techniques that target putative structural causes of non-specific low back pain polarises the clinical community and this controversy is well illustrated by the conflict between the Cochrane review<sup>103</sup> and the 2016 NICE draft guideline.<sup>91</sup> The detractors dismiss the validity of the tests used to identify the anatomical structure that is the “pain generator”, and point to the disappointing trial results.<sup>38,103,135</sup> The proponents counter that the negative studies should be ignored because they result from poor clinical care and argue that the positive studies show the potential of the treatments when applied to the right patients by skilled treatment providers.<sup>136,137</sup>

### Outstanding research questions

A major issue is how best to close the large gaps between evidence and practice that persist in the management of low back pain. The many attempts worldwide to influence clinical practice and improve uptake of evidence into routine management have yielded disappointing results. A systematic review of 17 qualitative studies investigating

barriers to clinician adherence to low back pain guidelines reported that clinicians believe that guidelines constrain professional practice, popular clinical practices supersede the guidelines, and imaging can be used to manage consultations.<sup>58</sup> Patient expectations, reimbursement schedules, and access to care might also contribute to gaps between evidence and practice. Patients’ perceptions seem to indicate poor content knowledge, methodological understanding, and trust in how guidelines are developed. Few implementation trials have been done,<sup>138</sup> and the published trials have shown disappointing results.<sup>139</sup> Another strategy that has yielded mixed results is use of public health approaches such as mass media campaigns that aim to shift low back pain beliefs of the whole population.<sup>140,141</sup>

Probably the greatest outstanding research priority draws from the question that clinicians face every day from their patients: what is causing my low back pain? A key limitation of existing management of non-specific low back pain is that it is only possible to use generic treatments to address the pain and its consequences. Although this approach works to some degree, the effect sizes for treatments are at best modest. The identification of low back pain phenotypes with either an identified pathoanatomical basis, or defined through clinical reasoning, will probably open up new approaches to management that directly target the cause of the low back pain and its consequent disability. This understanding has the potential to help the many people with disabling low back pain worldwide.

#### Contributors

All authors contributed equally to the Seminar.

#### Declaration of interests

CM is chief investigator or associate investigator on multiple previous and current research grants from government research agencies from Australia (eg, NHMRC), Brazil (eg, FAPESP), and the Netherlands (eg, ZonMW). For the past 10 years his salary has been covered by research fellowships from Australia’s National Health and Medical Research Council and the Australian Research Council. His research has also received funding from philanthropy (eg, Arthritis Australia) and government agencies (eg, NSW WorkCover). He has received travel expenses for speaking at conferences from the professional associations hosting the conferences, and has received honoraria for talks from professional associations and industry hosting the talks, honoraria for reviewing grants from government grant agencies, and honoraria for marking theses from the relevant university. CM has received supplementary industry funding for two investigator-initiated NHMRC-funded trials. The first trial had co-funding from GlaxoSmithKline. Pfizer provided the study medicine for the second trial, PRECISE, at no cost, but provided no other funding. MU is Chair of the NICE accreditation advisory committee for which he receives an honorarium. He was chair of the guideline development group that produced the 2009 NICE back pain guidelines. He is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health Research. He has completed trials of manual therapy, group exercise, and a cognitive behavioural approach as treatments for low back pain. Current grants include HTA Project 11/31/01, which is testing the feasibility of running a trial comparing intra-articular facet joint injections with best usual care. He is an editor of the NIHR journal series for which he receives a fee. RB is chief investigator or associate investigator on multiple previous and current research grants from government research agencies from Australia (eg, NHMRC, ARC), and overseas (eg, ZonMW in the Netherlands and PCORI in the USA). Her research has also received



funding from philanthropy (eg, Arthritis Australia) and government agencies (eg, NSW WorkCover). She has been funded by research fellowships from NHMRC since 2005. She has received travel expenses for speaking at conferences from the professional organisations hosting the conferences. She chaired the back pain expert group for the 2010 Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study. She was appointed to the Australian Medical Services Advisory Committee in May, 2016.

## References

- Hoy D, Bain C, Williams G, et al. A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012; **64**: 2028–37.
- Hoy D, March L, Brooks P, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; **73**: 968–74.
- Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386**: 743–800.
- Ferreira ML, Machado G, Latimer J, Maher C, Ferreira PH, Smeets RJ. Factors defining care-seeking in low back pain—a meta-analysis of population based surveys. *Eur J Pain* 2010; **14**: 747e1–7.
- Swain MS, Henschke N, Kamper SJ, Gobina I, Ottova-Jordan V, Maher CG. An international survey of pain in adolescents. *BMC Public Health* 2014; **14**: 447.
- Hestbaek L, Leboeuf-Yde C, Kyvik KO. Is comorbidity in adolescence a predictor for adult low back pain? A prospective study of a young population. *BMC Musculoskelet Disord* 2006; **7**: 29.
- Coenen P, Gouttebarger V, van der Burght AS, et al. The effect of lifting during work on low back pain: a health impact assessment based on a meta-analysis. *Occup Environ Med* 2014; **71**: 871–77.
- Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between smoking and low back pain: a meta-analysis. *Am J Med* 2010; **123**: 87e7–35.
- Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between obesity and low back pain: a meta-analysis. *Am J Epidemiol* 2010; **171**: 135–54.
- Pinheiro MB, Ferreira ML, Refshauge K, et al. Symptoms of depression and risk of new episodes of low back pain: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2015; **67**: 1591–603.
- Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008; **8**: 8–20.
- Walker BF, Muller R, Grant WD. Low back pain in Australian adults: the economic burden. *Asia Pac J Public Health* 2003; **15**: 79–87.
- Schofield DJ, Callander EJ, Shrestha RN, Passey ME, Kelly SJ, Percival R. Back problems, comorbidities, and their association with wealth. *Spine J* 2015; **15**: 34–41.
- Schofield DJ, Shrestha RN, Passey ME, Earnest A, Fletcher SL. Chronic disease and labour force participation among older Australians. *Med J Aust* 2008; **189**: 447–50.
- Schofield DJ, Shrestha RN, Percival R, Callander EJ, Kelly SJ, Passey ME. Early retirement and the financial assets of individuals with back problems. *Eur Spine J* 2011; **20**: 731–36.
- Froud R, Patterson S, Eldridge S, et al. A systematic review and meta-synthesis of the impact of low back pain on people's lives. *BMC Musculoskelet Disord* 2014; **15**: 50.
- MacNeela P, Doyle C, O'Gorman D, Ruane N, McGuire BE. Experiences of chronic low back pain: a meta-ethnography of qualitative research. *Health Psychol Rev* 2015; **9**: 63–82.
- Bunzli S, Watkins R, Smith A, Schutze R, O'Sullivan P. Lives on hold: a qualitative synthesis exploring the experience of chronic low-back pain. *Clin J Pain* 2013; **29**: 907–16.
- Snelgrove S, Liossi C. Living with chronic low back pain: a metasynthesis of qualitative research. *Chronic Illn* 2013; **9**: 283–301.
- Henschke N, Maher CG, Refshauge KM, et al. Characteristics of patients with acute low back pain presenting to primary care in Australia. *Clin J Pain* 2009; **25**: 5–11.
- Steffens D, Ferreira ML, Latimer J, et al. What triggers an episode of acute low back pain? A case-crossover study. *Arthritis Care Res (Hoboken)* 2015; **67**: 403–10.
- Parreira Pdo C, Maher CG, Latimer J, et al. Can patients identify what triggers their back pain? Secondary analysis of a case-crossover study. *Pain* 2015; **156**: 1913–19.
- Steffens D, Maher CG, Li Q, et al. Effect of weather on back pain: results from a case-crossover study. *Arthritis Care Res (Hoboken)* 2014; **66**: 1867–72.
- Duong V, Maher CG, Steffens D, Li Q, Hancock MJ. Does weather affect daily pain intensity levels in patients with acute low back pain? A prospective cohort study. *Rheumatol Int* 2016; **36**: 679–84.
- Waterman BR, Belmont PJ Jr, Schoenfeld AJ. Low back pain in the United States: incidence and risk factors for presentation in the emergency setting. *Spine J* 2012; **12**: 63–70.
- ISD Scotland. Back pain. 2016. <http://www.isdscotland.org/Health-Topics/General-Practice/GP-Consultations/Health-Conditions/Back-Pain/index.asp> (accessed July 6, 2016).
- Jarvik JG, Comstock BA, Heagerty PJ, et al. Back pain in seniors: the Back pain Outcomes using Longitudinal Data (BOLD) cohort baseline data. *BMC Musculoskelet Disord* 2014; **15**: 134.
- Hancock MJ, Maher CG, Latimer J, et al. Systematic review of tests to identify the disc, SIJ or facet joint as the source of low back pain. *Eur Spine J* 2007; **16**: 1539–50.
- Koes BW, van Tulder MW, Thomas S. Diagnosis and treatment of low back pain. *BMJ* 2006; **332**: 1430–34.
- Deyo RA, Weinstein JN. Low back pain. *N Engl J Med* 2001; **344**: 363–70.
- Henschke N, Maher CG, Refshauge KM, et al. Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. *Arthritis Rheum* 2009; **60**: 3072–80.
- Enthoven WT, Geuze J, Scheele J, et al. Prevalence and “red flags” regarding specified causes of back pain in older adults presenting in general practice. *Phys Ther* 2016; **96**: 305–12.
- Downie A, Williams CM, Henschke N, et al. Red flags to screen for malignancy and fracture in patients with low back pain: systematic review. *BMJ* 2013; **347**: f7095.
- Downie AS, Hancock MJ, Rzewuska M, Williams CM, Lin CW, Maher CG. Trajectories of acute low back pain: a latent class growth analysis. *Pain* 2016; **157**: 225–34.
- Underwood M, Buchbinder R. Red flags for back pain. *BMJ* 2013; **347**: f7432.
- Chou R, Qaseem A, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Diagnostic imaging for low back pain: advice for high-value health care from the American College of Physicians. *Ann Intern Med* 2011; **154**: 181–89.
- Intermountain Health. Primary care management of low back pain. August 2014. <https://intermountainhealthcare.org/ext/Dcmnt?ncid=522579081> (accessed July 6, 2016).
- Chou R. In the clinic. Low back pain. *Ann Intern Med* 2014; **160**: ICT6-1.
- Chou R, Fu R, Carrino JA, Deyo RA. Imaging strategies for low-back pain: systematic review and meta-analysis. *Lancet* 2009; **373**: 463–72.
- Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; **147**: 478–91.
- National Institute for Health and Clinical Excellence. Suspected cancer: recognition and referral. NICE guidelines [NG12]. 2015. <https://www.nice.org.uk/guidance/ng12> (accessed July 6, 2016).
- Li S, Peng Y, Weinhandl ED, et al. Estimated number of prevalent cases of metastatic bone disease in the US adult population. *Clin Epidemiol* 2012; **4**: 87–93.
- Goergen S, Maher C, Leech M, Kuang R. Acute low back pain. Education modules for appropriate imaging referrals: Royal Australian and New Zealand College of Radiologists, 2015. <http://www.ranzcr.edu.au/quality-a-safety/program/key-projects/education-modules-for-appropriate-imaging-referrals> (accessed July 6, 2016).
- van der Windt DA, Simons E, Riphagen II, et al. Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain. *Cochrane Database Syst Rev* 2010; **2**: CD007431.

- 45 Poddubnyy D, van Tubergen A, Landewe R, Sieper J, van der Heijde D; Assessment of SpondyloArthritis international Society (ASAS). Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. *Ann Rheum Dis* 2015; **74**: 1483–87.
- 46 Steffens D, Hancock MJ, Maher CG, Williams C, Jensen TS, Latimer J. Does magnetic resonance imaging predict future low back pain? A systematic review. *Eur J Pain* 2014; **18**: 755–65.
- 47 Koes BW, van Tulder M, Lin CW, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *Eur Spine J* 2010; **19**: 2075–94.
- 48 Williams CM, Maher CG, Hancock MJ, et al. Low back pain and best practice care: a survey of general practice physicians. *Arch Intern Med* 2010; **170**: 271–77.
- 49 Tan A, Zhou J, Kuo YF, Goodwin JS. Variation among primary care physicians in the use of imaging for older patients with acute low back pain. *J Gen Intern Med* 2016; **31**: 156–63.
- 50 Schlemmer E, Mitchiner JC, Brown M, Wasilevich E. Imaging during low back pain ED visits: a claims-based descriptive analysis. *Am J Emerg Med* 2015; **33**: 414–18.
- 51 Rizzardo A, Miceli L, Bednarova R, Guadagnin GM, Sbrojavacca R, Della Rocca G. Low-back pain at the emergency department: still not being managed? *Ther Clin Risk Manag* 2016; **12**: 183–87.
- 52 Rosenberg A, Agiro A, Gottlieb M, et al. early trends among seven recommendations from the choosing wisely campaign. *JAMA Intern Med* 2015; **175**: 1913–20.
- 53 Jame SZ, Sari AA, Majdzadeh R, Rashidian A, Arab M, Rahmani H. The extent of inappropriate use of magnetic resonance imaging in low back pain and its contributory factors. *Int J Prev Med* 2014; **5**: 1029–36.
- 54 Gidwani R, Sinnott P, Avoundjian T, Lo J, Asch SM, Barnett PG. Inappropriate ordering of lumbar spine magnetic resonance imaging: are providers choosing wisely? *Am J Manag Care* 2016; **22**: e68–76.
- 55 Hoffmann TC, Del Mar CB, Strong J, Mai J. Patients' expectations of acute low back pain management: implications for evidence uptake. *BMC Fam Pract* 2013; **14**: 7.
- 56 Jenkins HJ, Hancock MJ, Maher CG, French SD, Magnussen JS. Understanding patient beliefs regarding the use of imaging in the management of low back pain. *Eur J Pain* 2016; **20**: 573–80.
- 57 Buchbinder R, Staples M, Jolley D. Doctors with a special interest in back pain have poorer knowledge about how to treat back pain. *Spine (Phila Pa 1976)* 2009; **34**: 1218–26.
- 58 Slade SC, Kent P, Patel S, Bucknall T, Buchbinder R. Barriers to primary care clinician adherence to clinical guidelines for the management of low back pain: a systematic review and meta-synthesis of qualitative studies. *Clin J Pain* 2015; published online Dec 24. DOI:10.1097/AJP.0000000000000324.
- 59 Webster BS, Bauer AZ, Choi Y, Cifuentes M, Pransky GS. Iatrogenic consequences of early magnetic resonance imaging in acute, work-related, disabling low back pain. *Spine (Phila Pa 1976)* 2013; **38**: 1939–46.
- 60 Webster BS, Choi Y, Bauer AZ, Cifuentes M, Pransky G. The cascade of medical services and associated longitudinal costs due to nonadherent magnetic resonance imaging for low back pain. *Spine (Phila Pa 1976)* 2014; **39**: 1433–40.
- 61 Brinjikji W, Luetmer PH, Comstock B, et al. Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. *AJNR Am J Neuroradiol* 2015; **36**: 811–16.
- 62 Steffens D, Maher CG, Pereira LS, et al. Prevention of low back pain: a systematic review and meta-analysis. *JAMA Intern Med* 2016; **176**: 199–208.
- 63 Soukup MG, Glomsrod B, Lonn JH, Bo K, Larsen S. The effect of a Mensendieck exercise program as secondary prophylaxis for recurrent low back pain. A randomized, controlled trial with 12-month follow-up. *Spine (Phila Pa 1976)* 1999; **24**: 1585–91.
- 64 da C Menezes Costa L, Maher CG, Hancock MJ, McAuley JH, Herbert RD, Costa LO. The prognosis of acute and persistent low-back pain: a meta-analysis. *CMAJ* 2012; **184**: E613–24.
- 65 Henschke N, Maher CG, Refshauge KM, et al. Prognosis in patients with recent onset low back pain in Australian primary care: inception cohort study. *BMJ* 2008; **337**: a171.
- 66 Costa Lda C, Maher CG, McAuley JH, et al. Prognosis for patients with chronic low back pain: inception cohort study. *BMJ* 2009; **339**: b3829.
- 67 Stanton TR, Henschke N, Maher CG, Refshauge KM, Latimer J, McAuley JH. After an episode of acute low back pain, recurrence is unpredictable and not as common as previously thought. *Spine (Phila Pa 1976)* 2008; **33**: 2923–28.
- 68 Hayden JA, Chou R, Hogg-Johnson S, Bombardier C. Systematic reviews of low back pain prognosis had variable methods and results: guidance for future prognosis reviews. *J Clin Epidemiol* 2009; **62**: 781–96.e1.
- 69 Dahm KT, Brurberg KG, Jamtvedt G, Hagen KB. Advice to rest in bed versus advice to stay active for acute low-back pain and sciatica. *Cochrane Database Syst Rev* 2010; **6**: CD007612.
- 70 French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ. Superficial heat or cold for low back pain. *Cochrane Database Syst Rev* 2006; **1**: CD004750.
- 71 Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ* 2015; **350**: h1225.
- 72 Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev* 2008; **1**: CD000396.
- 73 Abdel Shaheed C, Maher C, Williams KA, McLachlan AJ. Efficacy and tolerability of muscle relaxants for low back pain: systematic review and meta-analysis. *Eur J Pain* 2016; published online Jun 22. DOI:10.1002/ejp.907.
- 74 Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev* 2013; **8**: CD004959.
- 75 Rubinstein SM, Terwee CB, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for acute low-back pain. *Cochrane Database Syst Rev* 2012; **9**: CD008880.
- 76 Furlan AD, Giraldo M, Baskwill A, Irvin E, Imamura M. Massage for low-back pain. *Cochrane Database Syst Rev* 2015; **9**: CD001929.
- 77 Hayden JA, van Tulder MW, Malmivaara A, Koes BW. Exercise therapy for treatment of non-specific low back pain. *Cochrane Database Syst Rev* 2005; **3**: CD000335.
- 78 Furlan AD, Yazdi F, Tsertsvadze A, et al. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. *Evid Based Complement Alternat Med* 2012; **2012**: 953139.
- 79 Main CJ, Buchbinder R, Porcheret M, Foster N. Addressing patient beliefs and expectations in the consultation. *Best Pract Res Clin Rheumatol* 2010; **24**: 219–25.
- 80 Main CJ, Foster N, Buchbinder R. How important are back pain beliefs and expectations for satisfactory recovery from back pain? *Best Pract Res Clin Rheumatol* 2010; **24**: 205–17.
- 81 O'Sullivan P, Lin IB. Acute low back pain. Beyond drug therapies. *Pain Management Today* 2014; **1**: 8–13.
- 82 Mannion AF, Wieser S, Elfering A. Association between beliefs and care-seeking behavior for low back pain. *Spine (Phila Pa 1976)* 2013; **38**: 1016–25.
- 83 Kongsted A, Vach W, Axo M, Bech RN, Hestbaek L. Expectation of recovery from low back pain: a longitudinal cohort study investigating patient characteristics related to expectations and the association between expectations and 3-month outcome. *Spine (Phila Pa 1976)* 2014; **39**: 81–90.
- 84 Engers A, Jellema P, Wensing M, van der Windt DA, Grol R, van Tulder MW. Individual patient education for low back pain. *Cochrane Database Syst Rev* 2008; **1**: CD004057.
- 85 Traeger AC, Hubscher M, Henschke N, Moseley GL, Lee H, McAuley JH. Effect of primary care-based education on reassurance in patients with acute low back pain: systematic review and meta-analysis. *JAMA Intern Med* 2015; **175**: 733–43.
- 86 Abdel Shaheed C, Maher C, Williams K, Day R, McLachlan AJ. Efficacy, tolerability and dose dependent effects of opioid analgesics for low back pain: systematic review and meta-analysis. *JAMA Intern Med* 2016; **176**: 958–68.
- 87 Chou R, Huffman LH; American Pain Society, American College of Physicians. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007; **147**: 505–14.

- 88 Friedman BW, Dym AA, Davitt M, et al. Naproxen with cyclobenzaprine, oxycodone/acetaminophen, or placebo for treating acute low back pain: a randomized clinical trial. *JAMA* 2015; **314**: 1572–80.
- 89 Deyo RA, Von Korff M, Duhkoop D. Opioids for low back pain. *BMJ* 2015; **350**: g6380.
- 90 Kea B, Fu R, Lowe RA, Sun BC. Interpreting the National Hospital Ambulatory Medical Care Survey: United States emergency department opioid prescribing, 2006–2010. *Acad Emerg Med* 2016; **23**: 159–65.
- 91 National Institute for Health and Care Excellence. Non-specific low back pain and sciatica: management. NICE guideline: short version. Draft for consultation, March 2016. <https://www.nice.org.uk/guidance/GID-CGWAVE0681/documents/short-version-of-draft-guideline> (accessed July 6, 2016).
- 92 Williams CM, Maher CG, Latimer J, et al. Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet* 2014; **384**: 1586–96.
- 93 Linton SJ, Nicholas M, MacDonald S. Development of a short form of the Orebro Musculoskeletal Pain Screening Questionnaire. *Spine (Phila Pa 1976)* 2011; **36**: 1891–95.
- 94 Hill JC, Whitehurst DGT, Lewis M, et al. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. *Lancet* 2011; **378**: 1560–71.
- 95 Hill JC, Dunn KM, Lewis M, et al. A primary care back pain screening tool: identifying patient subgroups for initial treatment. *Arthritis Rheum* 2008; **59**: 632–41.
- 96 Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev* 2016; **2**: CD012087.
- 97 Urquhart DM, Hoving JL, Assendelft WW, Roland M, van Tulder MW. Antidepressants for non-specific low back pain. *Cochrane Database Syst Rev* 2008; **1**: CD001703.
- 98 Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain. *Cochrane Database Syst Rev* 2011; **2**: CD008112.
- 99 Ebadi S, Henschke N, Nakhosin Ansari N, Fallah E, van Tulder MW. Therapeutic ultrasound for chronic low-back pain. *Cochrane Database Syst Rev* 2014; **3**: CD009169.
- 100 Khadilkar A, Odebiyi DO, Brosseau L, Wells GA. Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low-back pain. *Cochrane Database Syst Rev* 2008; **4**: CD003008.
- 101 Henschke N, Ostelo RW, van Tulder MW, et al. Behavioural treatment for chronic low-back pain. *Cochrane Database Syst Rev* 2010; **7**: CD002014.
- 102 Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. *Cochrane Database Syst Rev* 2014; **9**: CD000963.
- 103 Maas ET, Ostelo RW, Niemisto L, et al. Radiofrequency denervation for chronic low back pain. *Cochrane Database Syst Rev* 2015; **10**: CD008572.
- 104 Lee J, Gupta S, Price C, Baranowski AP; British Pain Society. Low back and radicular pain: a pathway for care developed by the British Pain Society. *Br J Anaesth* 2013; **111**: 112–20.
- 105 National Collaborating Centre for Primary Care. Low back pain: early management of persistent non-specific low back pain. London: National Institute for Health and Clinical Excellence, 2009. <https://www.nice.org.uk/guidance/cg88/evidence/full-guideline-243685549> (accessed July 6, 2016).
- 106 Airaksinen O, Brox JI, Cedraschi C, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006; **15** (suppl 2): S192–300.
- 107 Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: an update of the Cochrane review. *Spine (Phila Pa 1976)* 2014; **39**: 556–63.
- 108 Atkinson JH, Slater MA, Capparelli EV, et al. A randomized controlled trial of gabapentin for chronic low back pain with and without a radiating component. *Pain* 2016; **157**: 1499–507.
- 109 Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016; **315**: 1624–45.
- 110 Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 2015; **162**: 276–86.
- 111 Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med* 2010; **170**: 1979–86.
- 112 Cramer H, Lauche R, Haller H, Dobos G. A systematic review and meta-analysis of yoga for low back pain. *Clin J Pain* 2013; **29**: 450–60.
- 113 Yamato TP, Maher CG, Saragiotto BT, et al. Pilates for low back pain. *Cochrane Database Syst Rev* 2015; **7**: CD010265.
- 114 Saragiotto BT, Maher CG, Yamato TP, et al. Motor control exercise for chronic non-specific low-back pain. *Cochrane Database Syst Rev* 2016; **1**: CD012004.
- 115 Hollinghurst S, Sharp D, Ballard K, et al. Randomised controlled trial of Alexander technique lessons, exercise, and massage (ATEAM) for chronic and recurrent back pain: economic evaluation. *BMJ* 2008; **337**: a2656.
- 116 Little P, Lewith G, Webley F, et al. Randomised controlled trial of Alexander technique lessons, exercise, and massage (ATEAM) for chronic and recurrent back pain. *BMJ* 2008; **337**: a884.
- 117 Macedo LG, Smeets RJ, Maher CG, Latimer J, McAuley JH. Graded activity and graded exposure for persistent nonspecific low back pain: a systematic review. *Phys Ther* 2010; **90**: 860–79.
- 118 Hayden JA, van Tulder MW, Tomlinson G. Systematic review: strategies for using exercise therapy to improve outcomes in chronic low back pain. *Ann Intern Med* 2005; **142**: 776–85.
- 119 Furlan AD, van Tulder MW, Cherkin DC, et al. Acupuncture and dry-needling for low back pain. *Cochrane Database Syst Rev* 2005; **1**: CD001351.
- 120 Liu L, Skinner M, McDonough S, Mabire L, Baxter GD. Acupuncture for low back pain: an overview of systematic reviews. *Evid Based Complement Alternat Med* 2015; **2015**: 328196.
- 121 Lamb SE, Mistry D, Lall R, et al. Group cognitive behavioural interventions for low back pain in primary care: extended follow-up of the Back Skills Training Trial (ISRCTN54717854). *Pain* 2012; **153**: 494–501.
- 122 Maas E. Cost-effectiveness of radiofrequency denervation for chronic low back pain. PhD thesis, Vrije University Amsterdam, 2016.
- 123 Chou R, Hashimoto R, Friedly J, et al. Epidural corticosteroid injections for radiculopathy and spinal stenosis: a systematic review and meta-analysis. *Ann Intern Med* 2015; **163**: 373–81.
- 124 Dagenais S, Yelland MJ, Del Mar C, Schoene ML. Prolotherapy injections for chronic low-back pain. *Cochrane Database Syst Rev* 2007; **2**: CD004059.
- 125 Albert HB, Sorensen JS, Christensen BS, Manniche C. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *Eur Spine J* 2013; **22**: 697–707.
- 126 McCartney M. Antibiotics for back pain: hope or hype? *BMJ* 2013; **346**: f3122.
- 127 Mannion AF, Brox JI, Fairbank JC. Consensus at last! Long-term results of all randomized controlled trials show that fusion is no better than non-operative care in improving pain and disability in chronic low back pain. *Spine J* 2016; **16**: 588–90.
- 128 Michaleff ZA, Kamper SJ, Maher CG, Evans R, Broderick C, Henschke N. Low back pain in children and adolescents: a systematic review and meta-analysis evaluating the effectiveness of conservative interventions. *Eur Spine J* 2014; **23**: 2046–58.
- 129 Bishop FL, Dima AL, Ngui J, et al. “Lovely pie in the sky plans”: a qualitative study of clinicians’ perspectives on guidelines for managing low back pain in primary care in England. *Spine (Phila Pa 1976)* 2015; **40**: 1842–50.
- 130 Stanton TR, Hancock MJ, Maher CG, Koes BW. Critical appraisal of clinical prediction rules that aim to optimize treatment selection for musculoskeletal conditions. *Phys Ther* 2010; **90**: 843–54.
- 131 Hancock MJ, Kjaer P, Korsholm L, Kent P. Interpretation of subgroup effects in published trials. *Phys Ther* 2013; **93**: 852–59.
- 132 Mistry D, Patel S, Hee SW, Stallard N, Underwood M. Evaluating the quality of subgroup analyses in randomized controlled trials of therapist-delivered interventions for nonspecific low back pain: a systematic review. *Spine (Phila Pa 1976)* 2014; **39**: 618–29.
- 133 Hancock MJ, Maher CG, Latimer J, Herbert RD, McAuley JH. Independent evaluation of a clinical prediction rule for spinal manipulative therapy: a randomised controlled trial. *Eur Spine J* 2008; **17**: 936–43.

- 134 Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010; **340**: c117.
- 135 Vekaria R, Bhatt R, Ellard DR, Henschke N, Underwood M, Sandhu H. Intra-articular facet joint injections for low back pain: a systematic review. *Eur Spine J* 2016; **25**: 1266–81.
- 136 Datta S, Manchikanti L. Re: Chou R, Loeser JD, Owens DK, et al. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: an evidence-based clinical practice guideline from the American Pain Society. *Spine* 2009; **34**: 1066–77. *Spine (Phila Pa 1976)* 2010; **35**: 1826–27.
- 137 Boswell M, Abdi S, Manchikanti L. Misinterpretation of evidence synthesis and ASIPP guidelines by Chou. *Pain Med* 2009; **10**: 422–24.
- 138 Buchbinder R, Maher C, Harris IA. Setting the research agenda for improving health care in musculoskeletal disorders. *Nat Rev Rheumatol* 2015; **11**: 597–605.
- 139 French SD, McKenzie JE, O'Connor DA, et al. Evaluation of a theory-informed implementation intervention for the management of acute low back pain in general medical practice: the IMPLEMENT cluster randomised trial. *PLoS One* 2013; **8**: e65471.
- 140 Buchbinder R, Jolley D. Population based intervention to change back pain beliefs: three year follow up population survey. *BMJ* 2004; **328**: 321.
- 141 Buchbinder R, Jolley D, Wyatt M. Population based intervention to change back pain beliefs and disability: three part evaluation. *BMJ* 2001; **322**: 1516–20.