Question 1

What is the definition of substantial improvement according to the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT)?

a. ≥30% pain relief over baseline as assessed on a 0–10 numerical scale
b. ≥40% pain relief over baseline as assessed on a 0–10 numerical scale
c. ≥50% pain relief over baseline as assessed on a 0–10 numerical scale
d. ≥60% pain relief over baseline as assessed on a 0–10 numerical scale
e. ≥70% pain relief over baseline as assessed on a 0–10 numerical scale

Answer a. The NICE guideline recommends that pregabalin is a better treatment option than gabapentin because it has a lower NNH than gabapentin, a simpler dosing and titration regimen, the adverse-effect profiles of the two agents are similar, and health economic analysis suggests that pregabalin is more cost-effective than gabapentin. Direct head-to-head comparisons between gabapentin and pregabalin are lacking. Maximum licensed dose of gabapentin is 3,600mg per day.

Question 2

Mr RJ, 62 years old, has severe post-herpetic neuralgia. Amitriptyline failed to satisfactorily reduce his pain after 12 weeks. Mr RJ’s doctor has suggested a trial of gabapentin. Which one of the following statements regarding gabapentin is incorrect?

a. pregabalin has been shown to offer an advantage over gabapentin in the management of neuropathic pain in clinical trials that have directly compared the two drugs
b. gabapentin is licensed in the UK for the treatment of neuropathic pain
c. the National Institute for Health and Clinical Excellence (NICE) guideline considers that there is moderate- to high-quality evidence for the use of gabapentin in neuropathic pain
d. gabapentin has a higher number needed to treat than pregabalin
e. the maximum recommended dose of gabapentin is 3,600mg per day

Answer e. A systematic review found that for 17 people treated with an opioid, one person discontinued treatment because of adverse effects.

Question 3

Which one of the following statements about the management of neuropathic pain with opioids is correct?

a. the NICE guideline acknowledges that there is robust evidence to support the use of opioids
b. the risk of dependence is up to 50% in studies of chronic neuropathic pain
c. constipation diminishes with long-term use
d. long-term opioid therapy should not be prescribed in a non-specialist setting

Answer e. The guideline recommends that morphine and oxycodone should not be started in non-specialist settings without an assessment by a specialist pain service or a condition-specific service, although they suggest that treatment can be safely continued in a non-specialist setting provided that there is a multidisciplinary care plan, local shared care agreements, and careful management of adverse effects. The NICE guideline acknowledges that the evidence for the use and efficacy of opioids such as morphine and oxycodone is limited. Opioids carry the possibility of dependence in long-term use, the risk being up to 50% in studies of non-neuropathic chronic pain. Constipation is likely to be an ongoing problem that does not diminish with long-term use. The NNH for discontinuation of opioid treatment due to unwanted effects was 17 (95% CI: 9–100).
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Answers

An update on the drug treatment of neuropathic pain.
Part 2: antiepileptics and other drugs

Question 4
In a systematic review of carbamazepine, 66% of patients receiving carbamazepine and 27% of patients receiving placebo experienced at least one adverse event. What is the absolute risk increase and relative risk increase associated with taking carbamazepine?

a. 39%, 14.4%
b. 39%, 144%
c. 49%, 59%
d. 49%, 144%
e. 29%, 14.4%

Answer b. Taking carbamazepine increased the absolute risk of having at least one adverse event by 39 % and the risk relative to placebo by 144 %.

Question 5
Which one of the following statements about combination therapy is incorrect?

a. there is a risk of serotonin syndrome if tramadol is used in combination with duloxetine
b. there are relatively few studies of combination therapy
c. NICE makes no formal recommendations for the use of specific drug combinations in the non-specialist setting
d. topical capsaicin may be useful as an adjunctive therapy
e. tramadol should not be used as a rescue analgesic in combination with a second-line treatment

Answer e. The NICE guideline recommends tramadol as a third-line treatment for neuropathic pain in non-specialist settings, either as monotherapy or as a rescue analgesic in combination with a second-line treatment. There is a risk of serotonin syndrome when tramadol is used in combination with other serotonergic drugs, including SNRIs and SSRIs. On the basis of studies of combination therapy analysed in a NICE guideline, no formal recommendations are made for the use of specific drug combinations in non-specialist settings. Capsaicin had at best moderate efficacy, but it may be useful as an adjunctive therapy or monotherapy in patients who are either unresponsive to other treatments or intolerant of them.

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Mr WP, a 58-year-old with a 5-day history of severe diarrhoea, abdominal pain and fever, presents to the Accident and Emergency department. He is admitted to hospital and a stool sample confirms the diagnosis of *Clostridium difficile* infection (CDI). Between April 2011 and March 2012, approximately how many cases of CDI were reported in England?

a. 4,500  
b. 9,000  
c. 18,000  
d. 27,000  
e. 45,000

Answer c. A total of 18,005 cases of CDI occurring in patients aged 2 years and over were reported between April 2011 and March 2012 in England, equivalent to 35 per 100,000 population in England.

Mr WP had recently been started on a 2-week course of antibiotics following a bout of community-acquired pneumonia. Approximately what percentage of new cases of CDI is thought to originate outside hospital?

a. >20%  
b. >30%  
c. >40%  
d. >50%  
e. >60%

Answer c. Over 40% of new cases of CDI occur outside hospital.

Across Europe and North America, outbreaks of CDI with increased morbidity and mortality have been reported during the last decade, especially in older people. These outbreaks have been generally associated with the emergence and dissemination of a more virulent strain known as NAP1/BI/027. In the UK in what proportion of cases is this strain isolated?

a. 5%  
b. 25%  
c. 45%  
d. 65%  
e. 85%

Answer b. NAP1/BI/027 strain is only isolated in about 25% of cases in the UK.

To which class of antibiotics does fidaxomicin belong?

a. Lincosamide  
b. Tetracycline  
c. Aminoglycoside  
d. Macrocyclic  
e. Lipopeptide

Answer d. Fidaxomicin is the first antibiotic in a new class called macrocyclics.
Fidaxomicin for the treatment of Clostridium difficile infections

Question 5
Two multicentre double-blind randomised parallel-group non-inferiority studies have compared the safety and efficacy of fidaxomicin in patients with CDI. Which one of the following statements is correct?

a. The trials only included patients from USA and Canada
b. Patients received either fidaxomicin or metronidazole
c. The primary outcome measure was defined as the difference in recurrence rates between the two groups
d. The difference in recurrence rates for patients infected with the NAP1/BI/027 strain was statistically significant for the group of patients given fidaxomicin
e. Patients were excluded if they had had more than one episode of CDI in the previous 3 months

Answer e. The protocols were similar except that the first trial included 629 patients from USA and Canada, while the second trial also included people from Europe. Patients were included if they had more than 3 unformed stools in the 24 hours before randomisation, the presence of C. difficile toxins detectable within 48 hours of randomisation, and not more than 24 hours pre-treatment for CDI. Patients with fulminant or life-threatening CDI, multiple occurrences of CDI (more than 1 other episode in the previous 3 months), toxic megacolon, or Crohn’s disease were excluded. Patients received fidaxomicin 200 mg every 12 hours or vancomycin 125 mg every 6 hours for 10 days. The primary outcome measure was the clinical cure rate (clinical cure: resolution of diarrhoea [three or fewer unformed stools for 2 consecutive days] maintained for the duration of therapy and no further requirement for therapy for C. difficile infection as of the second day after the end of the course of therapy). The non-inferiority margin for the difference between treatment groups was –10 percentage points.

After early drop-outs, the modified intention-to-treat (mITT) populations (defined as patients with confirmed CDI who received at least 1 dose of trial medication) in the trials were 596 and 509 respectively. For the primary outcome of clinical cure rate, the 97.5% CI lower limit was well above the non-inferiority margin of –10%, demonstrating the non-inferiority of fidaxomicin relative to vancomycin. Subgroup analysis showed that recurrence rates in patients infected with the NAP1/BI/027 strain were similar in both treatment groups.