Perioperative Gabapentinoids

Choice of Agent, Dose, Timing, and Effects on Chronic Postsurgical Pain

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The gabapentinoids pregabalin and gabapentin are both indicated for the treatment of postherpetic neuralgia and as adjuvant therapy for seizure disorders. Pregabalin is additionally approved for the treatment of fibromyalgia and neuropathic pain associated with diabetes mellitus or spinal cord injury. There are now more than 100 clinical trials examining the use of gabapentin perioperatively to reduce postoperative pain and a smaller but growing number of clinical trials examining the efficacy of pregabalin. As a body of work, they support the conclusion that perioperative use of gabapentinoids reduces early postoperative pain and opioid use.¹⁻³ This article describes how this body of work may inform a surgeon’s or anesthesiologist’s optimization of perioperative use of gabapentinoids, including choice of agent, dose, timing, and duration of therapy. In addition, we described the less clear data for and against gabapentinoid efficacy in preventing the emergence of chronic postsurgical pain.

Mechanisms of Action, Pharmacokinetics, and Adverse Effects

Although both of the gabapentinoids are structural analogs of γ-aminobutyric acid, neither has any activity at the γ-aminobutyric acid receptors (fig. 1). Instead, they bind to the α₂β₃ subunit of presynaptic P/Q-type voltage-gated calcium channels, modulating the traffic and function of these channels. This in turn is thought to modulate the subsequent release of excitatory neurotransmitters from activated nociceptors.⁴ By modulating calcium-induced release of glutamate from activated pain-transmitting neurons, these drugs may inhibit pain transmission and central sensitization (fig. 2). Alternatively, some evidence indicates that their antinociceptive mechanism may arise through activation of noradrenergic pain-inhibiting pathways in the spinal cord and brain.⁵

The principal differences between these two drugs arise not from different modes of action but rather from differing bioavailability. Although both drugs are absorbed by amino acid carriers, gabapentin absorption is limited to a relatively small part of the duodenum, whereas pregabalin is absorbed throughout the small intestine. Once the active transport of gabapentin in the duodenum is saturated, progressively higher levels of gabapentin ingestion yield progressively smaller increases in blood concentrations. Conceptually, this provides an upper border not only to efficacy but also to adverse effects. In contrast, pregabalin appears to be absorbed throughout the small intestines and demonstrates linear uptake without transporter saturation at therapeutic concentrations.⁶⁻⁷ Therefore, at least conceptually, pregabalin might demonstrate both increased efficacy and increased side effects in situations that require high doses. Both pregabalin and gabapentin exhibit minimal protein binding and are renally excreted without significant metabolism. Pharmacokinetic interactions are minimal, though gabapentin absorption can be significantly impaired by antacids, even when given up to 2 h after dosing. This should be considered in preoperative
situations calling for the use of bicitra. The elimination half-life ranges of gabapentin and pregabalin are 4.8–8.7 h and 5.5–6.3 h, respectively. Dosing adjustments for both drugs must be considered in cases of renal dysfunction (table 1).

The gabapentinoids are generally very well tolerated. The most common side effects reported with pregabalin are sedation, dizziness or headache, and visual disturbances. In addition to sedation and dizziness, gabapentin users also report peripheral edema. Even massive overdoses of both drugs have been managed only with supportive care, typically on an outpatient basis. However, when continuing these agents postoperatively, these side effects should be sought and managed if needed through dose reduction. Interestingly, available data suggest that perioperative gabapentin actually reduces the likelihood of postoperative delirium and that pregabalin may reduce the incidence of vomiting. These effects may be mediated through a reduction in opioid use.

**Timing of Perioperative Dosing**

Human clinical trials of perioperative gabapentinoids support the belief that gabapentin is helpful in reducing acute postoperative pain and opioid consumption whether given preoperatively or postoperatively. At least two trials have directly compared the administration of gabapentin 2 h preoperatively versus immediately postincision via a nasogastric tube. Patients given gabapentin preoperatively as well as those given gabapentin immediately postincision both demonstrated lower visual analog scale scores at all time points and used less fentanyl compared with the placebo group. However, there was no difference in total opioid consumption or pain scores at any time point between the pre- and postincision gabapentin-treated groups. More recently, Cheung et al. used a

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**Fig. 1.** The gabapentinoids are not agonists at γ-aminobutyric acid (GABA) receptors.

**Fig. 2.** Hypothesized mechanisms of action of gabapentin. Gabapentin binds to the α2δ subunit of voltage-gated P/Q-type calcium channels. This binding appears to modulate the function and traffic of these channels which appear on the synaptic bulb of presynaptic neurons. Calcium influx through these channels after a pain-evoked action potential is believed to trigger the fusion of synaptic vesicles with the neuronal membrane and consequent release of neurotransmitters in the dorsal horn of the spinal cord. Gabapentin may exert its analgesic effect by inhibiting or modulating this process. In addition, gabapentin may exert an analgesic effect by activating descending inhibitory noradrenergic pathways that regulate neurotransmission of pain signals in the dorsal horn of the spinal cord.
crossover design to examine the efficacy of preoperative versus immediately postoperative administration of 75 mg of oral pregabalin. Patients were followed for 72 h after surgery, and the area under the curve for numerical rating scale in the first 24 h was significantly lower at rest for patients receiving postoperative pregabalin. However, the overall impression conveyed by their data was that any difference that exists between preoperative dosing and postoperative dosing appears to be quite small. Similarly, in a study that examined preoperative and postoperative gabapentin versus preoperative gabapentin alone, patients who received gabapentin postoperatively used significantly less morphine via patient-controlled analgesia at 24, 36, and 48 h. Patients who received gabapentin postoperatively also had significantly better active assisted knee flexion on postoperative day 2 and postoperative day 3 compared with those who received preoperative gabapentin alone. Furthermore, a Cochrane review that included data from four unpublished studies concluded that gabapentin is effective in already established acute postoperative pain even when dosed solely postoperatively. Thus, the existing data are at odds with preconceptions that preoperative dosing is critical for reducing immediate postoperative pain or opioid use. However, as detailed below, almost all of the studies assessing the potential long-term benefits of perioperative gabapentin did include preoperative dosing. For this reason, we conclude that such a preoperative dose is desirable, but the failure to give such a dose should not dissuade the clinician from postoperative dosing.

Most of the studies that have examined the preoperative administration of the gabapentinoids have administered the preoperative dose between 1 and 2 h before surgery. It has been reported that the time to peak plasma level after oral administration of gabapentin in humans is approximately 2 h and the time to peak plasma level after oral administration of pregabalin is approximately 1 h. However, it has also been reported that the time to peak cerebrospinal fluid level may be much longer. Among patients undergoing total knee replacement, peak cerebrospinal fluid levels of pregabalin occur at a median time of 8 h after administration. These data suggest that preoperative dosing may need to occur significantly earlier to exert its full opioid-sparing, pain-relieving (antihyperalgesic), and pain-preventing (preventative analgesia) effects.

### Optimal Perioperative Dose

The relatively few studies that have attempted to identify the optimal dose of gabapentin or pregabalin for perioperative use have generally enrolled too few patients per trial arm to make definitive recommendations (table 2 for summary) though the results have been promising. For example, Khan et al. studied 175 patients undergoing lumbar laminectomy and found that patients who received either 900 or 1,200 mg of gabapentin (either pre- or postoperatively) had lower pain scores throughout the entire first 24 h than patients who received either placebo or 600 mg of gabapentin.

### Table 1. Dosage Adjustments for Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance, ml/min</th>
<th>Maximum Daily Pregabalin Dose, mg</th>
<th>Maximum Daily Gabapentin Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>600</td>
<td>3,600</td>
</tr>
<tr>
<td>30–60</td>
<td>300</td>
<td>1,400</td>
</tr>
<tr>
<td>15–30</td>
<td>150</td>
<td>700</td>
</tr>
<tr>
<td>15</td>
<td>75</td>
<td>300</td>
</tr>
</tbody>
</table>

### Table 2. Studies Addressing Optimal Dose

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Surgery</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et al.</td>
<td>175</td>
<td>Laminectomy</td>
<td>Placebo, 600 mg, 900 mg, or 1,200 mg of gabapentin given preoperatively or postincision</td>
<td>Patients receiving either 900 or 1,200 mg had lower pain scores during the first 24 h compared with the 600 mg and placebo groups</td>
</tr>
<tr>
<td>Pandey et al.</td>
<td>100</td>
<td>Discectomy</td>
<td>Placebo, 300 mg, 600 mg, 900 mg, or 1,200 mg of gabapentin given 2 h preoperatively</td>
<td>Patients receiving ≥600 mg had lower visual analog scores at all time points compared with placebo or 300 mg groups</td>
</tr>
<tr>
<td>Van Elstraete et al.</td>
<td>67</td>
<td>Lumbar spinal fusion</td>
<td>Determination of optimal gabapentin dose for 30% reduction in morphine use by an up-and-down sequential allocation technique</td>
<td>Optimal dose for 30–50% reduction in morphine use calculated at 21.7 mg/kg (1,500 mg per 70 kg)</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>84</td>
<td>Lumbar spinal fusion</td>
<td>Placebo, 75 mg, or 150 mg of pregabalin preoperatively</td>
<td>Patient-controlled analgesia and adjuvant analgesic use were lower in the 150 mg group but not in the 75 mg group compared with placebo</td>
</tr>
<tr>
<td>Jokela et al.</td>
<td>90</td>
<td>Laparoscopic gynecological surgery</td>
<td>Active placebo, 75 mg of pregabalin, or 150 mg of pregabalin preoperatively</td>
<td>Pain scores at rest and in motion were lower in the 150 mg group but not the 75 mg group compared with placebo</td>
</tr>
</tbody>
</table>
These data were mirrored in 100 patients undergoing lumbar discectomy in which the authors found that patients who received either 600, 900, or 1,200 mg of gabapentin had lower visual analog scale scores at all time points than those receiving either placebo or gabapentin 300 mg.22 Similarly, a study on the optimal dose of gabapentin to reduce morphine consumption by 30% indicated that although lower doses of preoperative gabapentin (300–600 mg) may reduce postoperative pain and opioid use, higher doses (900–1,500 mg) may be even more effective.23

There also appears to be more significant efficacy with regard to reducing opioid consumption after surgery when higher doses of pregabalin are used. Two studies have found that 150 mg of pregabalin but not 75 mg of pregabalin was superior to placebo in reducing postoperative opioid consumption or pain scores.24,25 Overall, these data suggest that higher doses of preoperative gabapentin (1,200 mg) and pregabalin (300 mg) are significantly more effective than lower doses. Furthermore, continuing gabapentin or pregabalin postoperatively is likely more effective than a single preoperative dose of either gabapentinoids.

**Gabapentin or Pregabalin?**

Far more studies have been done examining the use of gabapentin perioperatively than of pregabalin in the same context. However, the single best study (in terms of adequate power and duration of follow-up) of perioperative gabapentinoids for reducing chronic pain was conducted using pregabalin.26

Three meta-analyses of adjunctive use of gabapentin for perioperative use have concluded that its use reduces early postoperative pain and opioid use after surgery.1–3 In contrast, a single meta-analysis from early 2010 examining the adjuvant use of pregabalin for surgical pain concluded that although it clearly reduced postoperative opioid use, there was insufficient evidence to state that it also reduced early postoperative pain scores.27 However, these results should be considered in light of the fact that only 5 of 45 articles on pregabalin for postoperative pain published between the years 2000 and 2010 had data that was included in this meta-analysis, and these studies included only 223 patients who received pregabalin.

At the time of writing this article, only two studies have examined the comparative effectiveness of gabapentin and pregabalin for the reduction of perioperative pain. In the first study, 90 patients undergoing laminectomy or discectomy were randomly assigned to receive study medication 2 h before surgery and 10 and 22 h after the operation. Study medication was either placebo, 150 mg of pregabalin, or 600 mg of gabapentin. Pregabalin and gabapentin were both superior to placebo in reducing the overall morphine consumption, preoperative anxiety, pruritus, as well as improving overall patient satisfaction. However, no difference in these measures was found between gabapentin and pregabalin.28 In a second study that examined 90 women undergoing abdominal hysterectomy, patients were randomized to receive 300 mg of pregabalin, 900 mg of gabapentin, or placebo 1–2 h before surgery. The pregabalin and gabapentin groups both had lower pain scores in the first hour after surgery, and these patients used smaller amounts of diclofenac compared with placebo. Pregabalin showed a greater decrease in pain intensity in the first hour after surgery than gabapentin, but was similar thereafter. The incidence of side effects was similar in the pregabalin and gabapentin groups.29 Unfortunately, there are no studies looking at long-term outcomes such as pain at 1 month, 3 months, or a year after surgery that compare gabapentin and pregabalin directly.

Another consideration in the choice of perioperative gabapentinoids is cost, as gabapentin is available in generic form, whereas pregabalin is still patent-protected. This cost difference can be significant if prolonged postoperative dosing is planned.

In conclusion, there is more and better overall evidence for choosing gabapentin to reduce early postoperative pain. However, there is sufficient evidence for clinicians to choose pregabalin as an alternative. The question of whether one agent is more efficacious or has fewer side effects would benefit from larger studies directly comparing the two drugs.

**Perioperative Gabapentinoids and Chronic Postsurgical Pain**

In general, studies examining the effect of perioperative gabapentin on persistent postsurgical pain have been limited by small sample size, limited follow-up, varied surgical populations, and widely varying dosing regimens. These regimens have included preoperative dosing only, postoperative only, or both pre- and postoperative dosing. The duration of postoperative dosing has varied from as little as one single postoperative dose to repeated dosing for as long as 30 days. Studies have also suffered from limited follow-up periods. The longest follow-up to evaluate effects on “chronic pain” was only 6 months.

At least 16 trials have been conducted examining the effect of perioperative gabapentinoids on long-term pain,26,30–44 with 9 demonstrating positive results (tables 3 and 4 for summary). Of note, the four trials of perioperative gabapentin that failed to identify any positive benefit were all markedly underpowered for that comparison. Therefore, the failure to find an effect should not be construed as strong evidence that an effect does not exist. In these studies, the number of patients per group that were available for long-term follow-up after taking perioperative gabapentin ranged from only 15 to 28.33,39,40,44

The single best-powered study examining the perioperative effect of gabapentinoids on persistent postsurgical pain was also conducted using pregabalin. Buvanendran et al. randomized 240 patients undergoing total knee replacements to receive either placebo or pregabalin 300 mg preoperatively, 150 mg twice a day for the first 10 days and 50 mg twice a day from days 10–14 after surgery. Most importantly, 6 months after surgery, 113 of the 120 patients initially randomized to pregabalin were still available for follow-up and were analyzed in their intent-to-treat analysis. Range of
motion was improved in the pregabalin group at 30 days after surgery, and the incidence of chronic postsurgical neuropathic pain was less frequent in the pregabalin group (0%) compared with the placebo group (8.7% and 5.2% at 3 and 6 months, respectively). Of note, the long-term reduction in pain produced by pregabalin was produced at the cost of increased sedation and confusion on the day of surgery in patients receiving pregabalin.26

Recently, Clarke et al.45 conducted a meta-analysis evaluating the combined trials of both pregabalin and gabapentin to prevent chronic postsurgical pain. They concluded that better designed and appropriately powered clinical trials are needed, but the combined data supported the view that perioperative administration of gabapentinoids is effective at reducing chronic postsurgical pain. These conclusions are weakened by the hazard of combining trials of different agents, doses, and durations in a single meta-analysis.

Overall, the data regarding the use of gabapentinoids to prevent chronic postsurgical pain are mixed. However, the studies that have failed to find an effect have generally been

### Table 3. Studies Finding an Effect on Prolonged Postoperative Pain

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Surgery</th>
<th>Gabapentinoid Dose</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fassoulaki et al.35</td>
<td>60</td>
<td>Abdominal hysterectomy</td>
<td>Gabapentin 400 mg every 6 h beginning preoperatively and continuing for 5 days</td>
<td>Decreased incidence and intensity of pain at 1 month</td>
</tr>
<tr>
<td>Sen et al.43</td>
<td>60</td>
<td>Herniorrhaphy</td>
<td>Gabapentin 1,200 mg 1 h before surgery</td>
<td>Decreased pain scores at 1, 3, and 6 months</td>
</tr>
<tr>
<td>Sen et al.42</td>
<td>60</td>
<td>Abdominal hysterectomy</td>
<td>Gabapentin 1,200 mg 1 h before surgery</td>
<td>Decreased incidence of incisional pain at 1, 3, and 6 months</td>
</tr>
<tr>
<td>Brogley et al.31</td>
<td>50</td>
<td>Thyroidectomy</td>
<td>Gabapentin 1,200 mg 2 h before surgery</td>
<td>Decreased incidence of neuropathic pain at 6 months</td>
</tr>
<tr>
<td>Amr and Yousef30</td>
<td>150</td>
<td>Mastectomy</td>
<td>Gabapentin 300 mg/day starting the night before surgery and continuing for 10 days</td>
<td>Decreased incidence of burning pain at 6 months</td>
</tr>
<tr>
<td>Fassoulaki et al.26</td>
<td>75</td>
<td>Breast surgery for cancer</td>
<td>Gabapentin 1,200 mg/day for 10 days after surgery</td>
<td>Decreased incidence of burning pain at 3 months</td>
</tr>
<tr>
<td>Buvanendran et al.26</td>
<td>240</td>
<td>Total knee arthroplasty</td>
<td>Pregabalin 300 mg 1–2 h before surgery and a 14-day taper after surgery</td>
<td>Decreased incidence of neuropathic pain at 3 and 6 months</td>
</tr>
<tr>
<td>Pesonen et al.41</td>
<td>70</td>
<td>Cardiac surgery</td>
<td>Pregabalin 150 mg 1 h before surgery and 150 mg daily for 5 days</td>
<td>Decreased incidence of pain with movement at 3 months</td>
</tr>
<tr>
<td>Burke and Shorten32</td>
<td>40</td>
<td>Lumbar discectomy</td>
<td>Pregabalin 300 mg 90 min before surgery and 150 mg at 12 and 24 h after surgery</td>
<td>Decreased pain scores and improved function at 3 months</td>
</tr>
</tbody>
</table>

### Table 4. Studies Finding No Effect on Prolonged Postoperative Pain

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Surgery</th>
<th>Gabapentinoid Dose</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ucak et al.44</td>
<td>40</td>
<td>Coronary artery bypass graft</td>
<td>Gabapentin 1,200 mg before and for 2 days after surgery</td>
<td>No difference in pain scores at 1 and 3 months (all scores ≤1)</td>
</tr>
<tr>
<td>Clarke et al.33</td>
<td>126</td>
<td>Total hip arthroplasty</td>
<td>Gabapentin 600 mg 1–2 h before surgery or 600 mg immediately postoperatively</td>
<td>No difference in presence or severity of pain at 6 months</td>
</tr>
<tr>
<td>Moore et al.39</td>
<td>44</td>
<td>Cesarean section</td>
<td>Gabapentin 600 mg 1 h before surgery</td>
<td>No difference in persistent pain or abnormal wound sensation at 3 months</td>
</tr>
<tr>
<td>Nikolajsen et al.40</td>
<td>41</td>
<td>Lower limb amputation</td>
<td>Gabapentin titrated to 2,400 mg/day beginning on the first postoperative day and continuing for 30 days</td>
<td>No difference in phantom or stump pain at 3 and 6 months</td>
</tr>
<tr>
<td>Giansello et al.37</td>
<td>60</td>
<td>Lumbar laminectomy and fusion</td>
<td>Pregabalin 300 mg 1 h before surgery for 2 days after surgery</td>
<td>No difference in pain scores at 3 months and 1 yr (quality of measures improved at 3 months)</td>
</tr>
<tr>
<td>Kim et al.38</td>
<td>94</td>
<td>Endoscopic thyroidectomy</td>
<td>Pregabalin 150 mg 1 h before surgery and at 12 h after surgery</td>
<td>No difference in pain or hyposthesia at 3 months</td>
</tr>
<tr>
<td>Fassoulaki et al.35</td>
<td>80</td>
<td>Abdominal hysterectomy or myomectomy</td>
<td>Pregabalin 150 mg every 8 h starting the afternoon before surgery and continuing 5 days</td>
<td>No difference in presence of pain, analgesic intake, or wound sensation at 1 and 3 months</td>
</tr>
</tbody>
</table>
small and underpowered. The more numerous positive studies have had only modest power as well, suggesting the effect size of gabapentinoids for preventing chronic pain may be quite substantial and clinically relevant. As suggested by the recent meta-analysis, it is now considerably more likely than not that gabapentinoids do have a preventative effect with regard to the formation of chronic postsurgical pain.

**Conclusion and Recommendations**

It should now be generally accepted that the gabapentinoids are effective in reducing immediate postoperative pain and opioid consumption. The clinician should recognize that this has been better established for gabapentin than pregabalin. However, larger studies with both longer follow-up and improved patient retention will be needed to more definitively test the efficacy of these agents to reduce the emergence of chronic postsurgical pain. When more studies on both pregabalin and gabapentin have been done assessing the effect of the gabapentinoids on chronic pain, another meta-analysis should examine the strength of the body of evidence as a whole. However, the currently available data support the conclusion that such a preventative analgesic effect is likely.

Further studies must also test the relative efficacy of gabapentin and pregabalin. Only then will the optimal gabapentinoid treatment become clear. Nonetheless, the existing studies suggest that higher preoperative doses and additional postoperative doses are advantageous in reducing immediate postsurgical pain. Failure to give a preoperative dose should not preclude the giving of intraoperative doses via nasogastric tube or postoperative doses alone.

Further definition of uncommon side effects, the optimal preoperative dose, postoperative dose, treatment duration, and timing of doses are needed before perioperative gabapentinoids can be recommended as the standard of care for all patients. However, we believe the current evidence is sufficient to recommend that either gabapentin 1,200 mg or pregabalin 300 mg should be given at least 2 h before surgery for patients at risk of developing either severe acute pain (e.g., the chronic opioid-consuming patient) or prolonged pain after surgery (e.g., thoracotomy). Either gabapentin or pregabalin should then be continued after surgery, but the optimal duration of treatment is unknown. The positive outcomes reported by Buvanendran suggest that continued dosing of gabapentinoids for 14 days after surgery is warranted. We recommend either postoperative gabapentin 600 mg thrice a day or pregabalin 150 mg twice a day (fig. 3). Postoperative gabapentinoid dosage should be decreased or stopped in the face of sedation, dizziness, or confusion. Given the evidence suggesting that it takes 8 h for pregabalin to reach peak cerebrospinal fluid level (and possibly 4–6 h for gabapentin to reach peak cerebrospinal fluid levels), it is possible that starting dosing the night before surgery may ultimately prove more beneficial than initiating dosing 2 h before surgery, but this effect may be at the risk of inducing dizziness, sedation, or confusion at home before surgery.

Fig. 3. Recommended dosing of perioperative gabapentinoids. Higher dose regimens appear more effective than lower dose regimens. Dosing may be initiated preoperatively, intraoperatively, or postoperatively—all three regimens have been shown to reduce early postoperative pain. Optimal duration of treatment is unknown, but studies with the most compelling outcomes have given gabapentinoids for up to 2 weeks. The single best study demonstrating reduction of chronic pain was accomplished with pregabalin; however, gabapentin has been studied perioperatively far more extensively. The overall data for reducing early postoperative pain and opioid use are most compelling for gabapentin. Either agents are appropriate and are recommended for patients at high risk of severe postoperative pain or chronic postsurgical pain.

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8. Lyrica [package insert]. New York, Parke-Davis, a Division of Pfizer, 2009
28. Ozgencel E, Yalcin S, Tuna H, Yorukoglu D, Keckik Y: Perioperative administration of gabapentin 1,200mg day−1 and pregabalin 300mg day−1 for pain following lumbar laminectomy and discectomy: A randomised, double-blinded, placebo-controlled study. Singapore Med J 2011; 52:883–9