Recent trials in neurology that should influence your practice

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Introduction

Neurology is a vast area encompassing diverse disease states, including multiple sclerosis, epilepsy, stroke and headache. These conditions affect individuals across the age spectrum and can be encountered in all practice settings. While neurology was once considered a subspecialty with few treatment options, today many therapies are available that can substantially improve physical function and quality of life. With an increase in an older population will come a greater prevalence of diseases of the aging brain, requiring clinicians to respond to the increasing demand for neurological care.¹ Each year, new studies are added to the existing literature pool in all of these various subspecialties, creating a challenge for busy clinicians to keep up with best practice for their patients. In this article, we summarize 5 recent neurology articles of importance to pharmacists to aid in the care of their patients.

Methods and Rationale

Through discussion with pharmacists practising in various areas of neurology across Canada, a list of potential studies published within the past 2 years and deemed to be of importance to frontline pharmacists was generated. The list was refined to the final 5 articles by the authors and select pharmacist experts. These trials and their potential impact on pharmacists and patients are summarized below.

The first 2 articles focus on stroke, a disease that affects approximately 50,000 Canadians per year and is the leading cause of disability in Canada, with approximately 300,000 citizens living with the negative effects of stroke.² The first trial, SPS3, tested 2 interventions in patients with

recent, symptomatic lacunar (small) stroke: 2 antiplatelet regimens and 2 blood pressure targets; the focus of this article will be the blood pressure arms.³ In the second trial, CHANCE, the authors looked at whether a short course of dual antiplatelet therapy could reduce this risk during the early treatment period.⁴

Headache is a common neurological complaint. Many patients self-medicate with over-the-counter medications, making them ideal candidates for pharmacist intervention.^{5,6} In addition to the official indication and evidence supporting the use of botulinum toxin (BTX) for treating chronic migraine, BTX prophylaxis is rising in popularity for other headache disorders. In the third article, a meta-analysis of this agent's use is reviewed for migraine and tension-type headache.⁷

Multiple sclerosis (MS) is a chronic, debilitating neurological condition affecting approximately 100,000 Canadians. MS is the most common neurological disease affecting young adults in this country, and Canadians are known to have one of the highest MS prevalence rates in the world.⁸ The theory that current autoimmune therapies may be misguided and the pathophysiology of this disease may be vascular in nature has been revisited in the past few years. In 2009, Zamboni and colleagues⁹ suggested that stenosis in the venous drainage system (referred to as "chronic cerebrospinal venous insufficiency," or CCVI) was significantly associated with MS and speculated that reversal of that venous blockage would ameliorate the disease. They further conducted an unblinded, uncontrolled interventional treatment which showed that venoplasty in affected

patients improved disability and quality of life in MS patients.¹⁰ This was heralded as a “miracle cure” in the media, and patients from Canada and elsewhere flocked overseas to participate in the “Liberation Therapy,” despite a lack of independent validation studies or consensus of the efficacy and safety of this procedure for this purpose. In the fourth article, Traboulsee and colleagues¹¹ set out to test the theory that venous narrowing was associated with MS.

Finally, status epilepticus, or prolonged epileptic seizures, is considered a medical emergency and is associated with a high mortality rate. Early termination of these seizures with intravenous (IV) benzodiazepines is associated with better patient outcomes.¹² In the fifth and final article, RAMPART investigators sought to determine whether intramuscular midazolam could be considered a suitable alternative to IV lorazepam.¹³

STROKE

Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomized trial (*Lancet* 2013)

Background: While it is known that lowering blood pressure prevents stroke, optimum targets to prevent recurrent stroke are unknown.

Purpose: The purpose of this randomized, open-label, multicentre study³ was to determine whether a lower systolic blood pressure target would be more effective than a higher target in preventing recurrent stroke in patients with recent lacunar stroke.

Patients: Patients included were aged 30 years or older, were normotensive or hypertensive (defined as blood pressure >140/90) and had had a recent (<180 days) symptomatic lacunar stroke. Exclusion criteria were disabling stroke, previous intracranial hemorrhage, cortical ischemic stroke or significant carotid stenosis or a cardioembolic source.

Intervention and control: Patients were randomized at least 2 weeks after a stroke via a 2-by-2 factorial design to 2 blood pressure control groups with systolic targets of either 130–149 mmHg or less, or less than 130 mm Hg. Antihypertensive medications were prescribed according to study formularies and could include drugs from each of the major classes.

Outcomes: The primary outcome was reduction in all-cause strokes. Secondary endpoints were reductions in myocardial infarction, need for hospitalization due to a major vascular event and death. Safety outcomes were serious adverse events related to hypotension and blood pressure management.

Results: A total of 3020 participants were enrolled and followed for a mean of 3.7 years. The average age was 63 years, and 63% of the patients were

male. Blood pressure at entry was 144/79 mmHg in the higher-target group (HTG) and 142/78 mmHg in the lower-target group (LTG), and there were no significant differences in baseline characteristics between the groups. At 1 year of follow-up, average systolic blood pressures were 138 mmHg (standard deviation [SD] 0.39 mmHg) in the HTG and 127 mmHg (SD 0.38 mmHg) in the LTG, with 75% and 65% of patients achieving targets, respectively. At 1 year and the last visit, the average number of antihypertensive medications was 1.8 (SD 1.4) in the HTG and 2.4 (SD 1.4) in the LTG. The annualized recurrent stroke rate was 2.77% in the HTG compared with 2.25% in the LTG (hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.64 to 1.03). Two prespecified subgroup analyses were performed: the first excluded normotensive patients and the second censored data prior to 6 months (assuming it took that long to achieve the blood pressure target). Both demonstrated similar hazard ratios, and neither demonstrated statistical significance between the HTG and LTG arms. There were no statistically significant differences in any of the secondary outcomes. There were fewer adverse effects related to hypotension in the HTG, but the difference was not statistically significant.

Implications for practice: The reduction in recurrent stroke (19%) between the groups was lower than the expected 25% to 30%, given the degree of blood pressure lowering, perhaps explaining in part why the primary outcome did not achieve statistical significance. Some clinicians may use the downward trend of the recurrent stroke rate and the lack of more serious adverse events in this study to justify targeting lower blood pressures in all patients. However, the clinical context of the patient, including falls risk, frailty, patient-desired outcomes and the ability to tolerate

or adhere to an aggressive treatment regimen and accompanying medication and monitoring burden, should continue to be considered.

Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE) (*N Engl J Med* 2013)

Background: As the first few weeks after minor stroke or transient ischemic attack (TIA) carry the highest risk of a recurrent event, there is a question of whether aggressive treatment can reduce this risk.

Purpose: The objective of this superiority trial⁴ was to determine whether treatment with the combination of aspirin (ASA) and clopidogrel would reduce the risk of recurrent stroke, as compared with aspirin alone, in patients with acute minor ischemic stroke or high-risk TIA. This randomized, double-blind, double-dummy, placebo-controlled trial was completed across multiple clinical centres in China.

Patients: Included were patients 40 years of age and older with diagnosed acute minor ischemic stroke or high-risk TIA who were able to start the study drugs within 24 hours of symptom onset. The exclusion criteria included patients with hemorrhage; major nonischemic brain disease; isolated sensory, visual, or dizziness or vertigo symptoms without evidence of acute infarction on computed tomography or magnetic resonance imaging; modified Rankin score greater than 2 (indicating a more severe stroke); indication for anticoagulation therapy; contraindication to study drug; history of intracranial hemorrhage; need for long-term nonstudy antiplatelet or nonsteroidal anti-inflammatory drugs (NSAIDs); gastrointestinal (GI) bleeding; and major surgery within the last 3 months.

Intervention and control: For the 90-day trial period, patients were randomized to receive either

clopidogrel plus ASA for 21 days, then clopidogrel plus placebo, or placebo plus ASA. The ASA dose used was 75 to 300 mg on day 1 followed by 75 mg daily. The clopidogrel dose used was 300 mg on day 1 followed by 75 mg daily. Randomization was stratified by clinical centre and interval between symptom onset and enrollment (<12 hours vs 12–24 hours).

Outcomes: The primary efficacy outcome was new stroke event (ischemic or hemorrhagic) at 90 days. The primary safety outcome was any moderate to severe bleeding event.

Results: A total of 5170 patients were enrolled and followed for 90 days. The mean age was 62 years, 33.8% were female and 27.9% of patients had TIA as the reason for inclusion. The occurrence of a new stroke event was significantly less for patients taking ASA plus clopidogrel (8.2%) than patients taking ASA monotherapy (11.7%) (HR = 0.68; $p < 0.001$). The reduction in new stroke events with combination therapy was consistent in all prespecified subgroups. The primary safety outcomes (severe or moderate bleeding, intracranial hemorrhage) were not significantly different between the 2 groups.

Implications for practice: This trial demonstrated that the combination of ASA and clopidogrel reduced the rate of new stroke event in patients with acute high-risk TIA or minor ischemic stroke compared with ASA alone. As patients were treated within 24 hours of symptom onset, and because the first few days of treatment saw dramatic divergence of the curves representing survival free of stroke, early intervention with combination therapy may likely derive the greatest benefit. As the patients randomized in this trial were at high risk of recurrent ischemia and were treated only in China, the treatment effect may vary in other populations.

HEADACHE

Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis (*JAMA* 2012)

Background: In Canada and the United States, botulinum toxin (BTX) has an official indication for the prophylaxis of chronic migraines. This indication is based primarily on the placebo-controlled phase II research evaluating migraine prophylaxis therapy (PREEMPT) trials. These 2

trials showed positive results with BTX; however, these results are inconsistent with other BTX studies. In addition, clinicians have used BTX off-label for other types of headache.

Purpose: This meta-analysis⁷ was conducted to determine the benefit of using BTX for prophylaxis in the treatment of migraine (chronic or episodic) or tension type headaches (TTH) (chronic daily, or episodic).

Intervention and control: Standard methodology was used for meta-analysis, following the PRISMA guidelines.¹⁴ Randomized controlled trials were included if they enrolled adults and were at least 4 weeks long.

Outcomes: Standard patient-reported outcomes for headache trials were evaluated, including reduced frequency of headaches and reduced severity of headaches (50% reduction in severity).

Results: A total of 31 trials were included ($n = 5313$). The participants were mostly female (76%), with a mean age of 42 years. The BTX protocols varied in the dose (BTX units) and in the site and number of injections (i.e., between 4 and 58 injections per treatment at various sites). Twenty of the placebo-controlled trials used fixed-site administration, while 7 studies used a “follow the pain” approach to injection. With the use of BTX, there was a 2.06 reduction in number of chronic daily headaches per month (95% CI -3.56 to -0.56) and a 2.30 reduction in chronic migraines per month when compared with placebo (95% CI -3.66 to -0.94). There was an absolute reduction from 19.5 to 17.2 headaches per month for chronic migraine and from 17.5 to 15.4 for chronic daily headaches. For episodic migraine or TTH, there was no significant reduction in number of headaches.

Of 31 trials, 8 considered the outcome of severity (50% improvement). Of these, only chronic migraine showed a significant reduction in severity (relative risk [RR] = 2.21; 95% CI 1.30 to 3.78).

Of the 31 trials, 4 compared BTX to another drug therapy and found that in chronic

migraine, BTX was not superior to topiramate or amitriptyline in terms of headache frequency. Additionally, BTX was not superior to valproate in reducing frequency of chronic or episodic migraine. However, in chronic TTH, BTX was superior to methylprednisolone (-2.5 headaches per month; 95% CI -3.5 to -1.5).

Subjects receiving BTX reported significantly more adverse events, although they withdrew from the study as frequently as did control subjects. The most commonly reported adverse events were blepharoptosis (RR 9.5; 95% CI 4.7 to 18.9), muscle weakness (RR 8.9; 95% CI 2.5 to 30.9), neck pain (RR 4.7; 95% CI 3.2 to 6.9), neck stiffness, paresthesias and skin tightness.

Implications for practice: There may be a relative benefit to using BTX for prophylaxis to reduce frequency of headaches in chronic migraine and chronic daily headache compared with placebo treatments, although the absolute reductions are marginal. Based on the results of 1 trial only, the severity of chronic migraines may be reduced with BTX use. The few comparative trials indicate that BTX may not be superior to other, older therapies. Further research is required to establish the most effective dose and injection protocols. The adverse events were predictable and did not result in increased rates of withdrawal compared with placebo. Patients may consider using BTX when other therapies are ineffective or intolerable, although further research is required to determine the optimal dosing regimen and administration protocol for BTX in headache disorders.

MULTIPLE SCLEROSIS

Prevalence of extracranial venous narrowing on catheter venography in people with multiple sclerosis, their siblings, and unrelated healthy controls: a blinded, case-control study (Lancet 2014)

Background: The pathophysiology of multiple sclerosis (MS) remains uncertain, and a vascular mechanism has been previously hypothesized.

Purpose: The purpose of this assessor-blinded, case-control, multicentre study¹¹ was to establish the prevalence of venous narrowing in people with MS, unaffected siblings (siblings of MS patients have higher risk of MS) and unrelated healthy controls.

Patients: Study subjects included patients with MS, their healthy siblings and unrelated healthy controls aged 18 to 65 years. Patients who had previously undergone venous procedures were excluded.

Intervention and control: All participants received a blinded standardized catheter venography procedure with standard definitions for hemodynamically significant narrowing or stenosis ($>50\%$ narrowing) of the jugular or azygos veins. Venous Doppler ultrasound equipment was identical to that used by Zamboni, and experienced ultrasonographers were trained by Zamboni in Italy.⁹ The venous Doppler

Zamboni definitions for CCVI were used, and this procedure was also blinded. Studies were performed in 3 Canadian centres.

Outcomes: The primary aim was to clarify whether venous blockages are unique to patients with MS by establishing the prevalence of venous narrowing in the study subjects. The secondary aim was to assess the sensitivity and specificity of the Zamboni Doppler ultrasound criteria for CCVI compared with catheter venography.

Results: The study included 79 patients with MS, 55 unaffected siblings and 43 unrelated healthy controls (totaling 98 health controls) with a similar mean age (47.8 vs 48.7) and proportion of women (85% vs 72%) in each group. The median disease duration was 13 years (range 2-41 years) and the median Expanded Disability Status Score (EDSS) was 2.0 (range 0-6.5), indicating a relatively ambulatory patient who can perform most of his or her daily activities without aid. Catheter venography data were available for 149 participants and ultrasound data for 171 participants. Catheter venography criteria for CCVI were met in 1 of 65 (2%) people with MS, 1 of 46 (2%) siblings and 1 of 32 (3%) unrelated controls ($p = \text{not significant [NS]}$ for

all comparisons). Greater than 50% narrowing of any major vein was found in 48 of 65 (74%), 31 of 47 (66%) and 26 of 37 (70%) subjects in these groups, respectively ($p = \text{NS}$ for all comparisons). Ultrasound criteria for CCVI were met in 35 of 79 (44%) MS patients, 17 of 54 (31%) unaffected siblings and 17 of 38 (45%) unrelated controls ($p = \text{NS}$ for all comparisons). The sensitivity of the ultrasound criteria for detection of greater than 50% narrowing on catheter venography was 0.406 (95% CI 0.311 to 0.508) and specificity was 0.643 (95% CI 0.480 to 0.780).

Implications for practice: Being highly accessible health care professionals, pharmacists may field inquiries from patients regarding the validity of the “liberation procedure” in MS patients. This study demonstrates that CCVI occurs rarely both in patients with MS and in healthy people. Extracranial venous narrowing occurs frequently in patients with MS and otherwise healthy people. Ultrasound is a poor substitute for demonstrating true narrowing, and the overall link between venous narrowing and MS remains unestablished. Procedures to “reverse” venous narrowing to improve MS symptoms cannot be recommended based on the available evidence.

EPILEPSY

Intramuscular versus intravenous therapy for prehospital status epilepticus (*N Engl J Med* 2012)

Background: While lorazepam remains the drug of choice for status epilepticus, it is rarely used outside of hospital due to difficulties in attaining IV access and its short shelf-life outside of the refrigerator. For faster and more reliable administration, paramedics are increasingly using an intramuscular route with midazolam, despite a lack of clinical trial data regarding its efficacy and safety.

Purpose: The purpose of this randomized, multicentre, double-blind, noninferiority trial¹³ was to investigate whether intramuscular midazolam (IM-M) was noninferior to intravenous lorazepam (IV-L) for early termination of prolonged seizures.

Patients: Included were children weighing at least 13 kg and adults experiencing convulsive seizures for a minimum of 5 minutes in a prehospital

setting. Excluded were patients with seizures precipitated by major trauma, hypoglycemia, cardiac arrest or bradycardia; those allergic to midazolam or lorazepam; those known to be pregnant or a prisoner; those being treated as part of another study; or those who had previously opted out of the study by wearing a bracelet marked “RAMPART declined.”

Intervention and control: Patients were randomized to receive either IM-M 10 mg (5 mg for patients 13-40 kg) followed by placebo IV-L, or placebo IM-M followed by IV-L 4 mg (2 mg for patients 13-40 kg).

Outcomes: The primary efficacy outcome was absence of seizures at the time of arrival to the emergency department (ED) without the need for rescue therapy. Secondary and safety outcomes included the need for endotracheal intubation, acute recurrent seizures, the timing of treatment relative to cessation of seizure, the time from study-box opening to seizure cessation and the

frequency and duration of hospitalization and admission to the intensive care unit (ICU).

Results: A total of 893 patients were included in the intention-to-treat analysis. Fifty-six percent were male, with a median age of 43 years. Upon arrival to the ED, seizures were absent with no rescue therapy in 73.4% of midazolam patients and in 63.4% of lorazepam patients ($p < 0.001$). The secondary outcomes were matched for endotracheal intubation (14.1% IM-M vs 14.4% IV-L) and for acute recurrent seizures (11.4% IM-M vs 10.6% IV-L). The patients randomized to IM-M had significantly lower rates of hospitalization (57.6% IM-M vs 65.5% IV-L) and of ICU admission (28.6% IM-M vs 36.2% IV-L). The time to administration was significantly shorter for IM-M than for IV-L (1.2 vs 4.8 minutes), but the time to termination of convulsion was shorter for IV-L (3.3 vs 1.6 minutes). Of note, 5 patients did not receive the

IM-M due to autoinjector malfunction, whereas the inability to start an IV-L infusion occurred for 31 patients.

Implications for practice: For patients in status epilepticus, IM-M was noninferior to IV-L for prehospital seizure cessation. Based on this research, giving a dose of IM-M via autoinjector is a fast, effective and reliable method to terminate seizures en route to hospital. IM-M may be the treatment of choice due to stability at room temperature, improved injection techniques and quicker time to administration. For health professionals (e.g., paramedics) who may be required to use medication to terminate seizure activity as quickly as possible, intramuscular midazolam may be considered a reasonable first-line agent. While a midazolam autoinjector is not currently available in Canada, companies are pursuing development of such a device in the United States. ■

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