Multiple Sclerosis (MS) is the most common disabling neurological disease of young adults, especially in Canada, where the overall prevalence is 240/10,0001. Most (85%) patients are diagnosed with relapsing remitting (RR) MS at presentation2 and up to 40% of secondary progressive (SP) MS patients continue to have relapses3. Corticosteroid treatment may improve the speed of functional recovery with acute MS relapses but does not provide any long-term functional benefit4. There is currently no compelling evidence that the clinical benefit of high dose corticosteroids is influenced by the route of administration, the particular corticosteroid prescribed, or the dosage of corticosteroid5,6. Traditionally, intravenous (IV) administration of corticosteroid preparations has been used, but oral therapy is less expensive and more convenient for the patient7. Recent studies have supported the bioequivalent and clinical equivalence of high dose oral corticosteroids for MS relapses8,9, and a recent Cochrane review found no evidence to support one regimen as superior10. Furthermore, studies support the gastric safety of high dose oral steroids11. Oral administration is considered more suitable by MS patients, as it avoids traveling...
Almost all subjects (49, 92.5%) were treated with five days of 1250mg oral prednisone without a tapering dose. The reported compliance rate was high at 94.3% (50/53). Only one patient reported being unable to take all the required pills due to intolerance and thus was switched to IV corticosteroids; two subjects did not return the survey. The majority (45, 90.0%) of patients reported taking the 25 pills all at once, while 7 subjects (14.0%) divided the pills into two doses and one subject divided the pills into three doses throughout the day. Most subjects (43, 86.0%) encountered at least one side effect. The most common side effects reported were insomnia (36, 83.7%), mood changes, described as irritability, agitation or euphoria (28, 65.1%), and increased appetite (15, 34.9%) (Table 1).

More than half the cohort had been treated with corticosteroids in the past for a previous relapse (32, 60.4%) and of those subjects, 18 (56.3%) had received oral corticosteroids at least once. When asked regarding preference of route of administration of corticosteroids for future relapses, 37 (69.8%) indicated a preference for oral medication, four (7.5%) preferred IV medication while another four (7.5%) indicated no preference (eight subjects did not respond).

### Discussion
Corticosteroids have been used to treat acute demyelinating events for many years, improving the speed of functional recovery, but without any clear long-term impact on degree of recovery or disease course	extsuperscript{12}. This study demonstrates that compliance with high doses of oral prednisone is not an issue when treating acute demyelinating events such as MS relapses. Administration of corticosteroids intravenously became the standard of practice based on the results of the Optic Neuritis Treatment Trial (ONTT)	extsuperscript{12}. In this study, the IV methylprednisolone group had a higher rate of return of vision than the placebo group while the oral prednisone group did not. Additionally, treatment with oral prednisone was associated with a higher risk of new episodes of optic neuritis than both the IV and placebo group. However, the treatment groups were not equivalent. The IV group received 1000mg of methylprednisolone daily for three days followed by an oral taper over 11 days, while the prednisone group received a much lower daily dose: 1mg/kg daily for 14 days. Yet, these results have influenced how physicians treat optic neuritis, as demonstrated by the results of this study.

### Methods
Between November 1 2008 and December 31 2009, any patient of the London MS clinic, in London, Ontario, Canada assessed for a potential relapse, either by telephone contact or clinic visit, was identified by the treating clinician. Once a relapse has been confirmed and the treatment plan initiated, patients treated with oral prednisone as an outpatient were offered participation in this prospective survey study. Patients who required hospitalization or were treated with IV corticosteroids were not approached to participate; however, a tally was kept of the total number of patients treated for a relapse. A one page (two-sided) questionnaire was given to patients with the oral prednisone prescription. The questionnaire was anonymous; he/she was given an unmarked postage-paid return envelope. Each subject was only included in the study once. If he/she had more than one relapse treated with oral corticosteroids during the study, the patient was approached to participate during the first relapse only. One week after the initial contact, a clinic staff member called to remind the participant to return the questionnaire, without addressing the patient’s compliance to the medication or coercing the patient to participate. Data collected included demographic information, type of MS, and data regarding the patient compliance with the medication as well as any reasons why he/she could not comply with the medication instructions. This study was approved by the university’s research ethics board.

### Results
Sixty-eight relapses in 66 patients were treated for an acute relapse during the study, of which eight were treated with IV corticosteroid. Thus, 58 subjects were invited to participate in the study. All patients treated with oral corticosteroids agreed to participate and were given the survey, however, only 53 (91.4%) surveys were returned. There were 34 (64.2%) women in this sample, with the following age distribution: two (3.8%) < 20 years, 9 (17.0%) 21-30 years, 19 (35.8%) 31-40 years, 17 (32.1%) 41-50 years and 6 (11.3%) >50 years old. Most of the patients identified themselves as relapsing remitting MS (46, 86.8%) while three (5.7%) had a diagnosis of clinically isolated syndrome. The average disease duration was 7.0 years.

### Table 1: Reported Adverse Events Associated with oral prednisone for relapse treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N</th>
<th>% of subjects who reported adverse events</th>
<th>% of total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>36</td>
<td>83.7%</td>
<td>67.9</td>
</tr>
<tr>
<td>Mood changes</td>
<td>28</td>
<td>65.1%</td>
<td>52.8</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>15</td>
<td>34.9%</td>
<td>28.3</td>
</tr>
<tr>
<td>Nausea or GERD</td>
<td>9</td>
<td>20.9%</td>
<td>17.0</td>
</tr>
<tr>
<td>Horrible taste of pills</td>
<td>3</td>
<td>7.0%</td>
<td>5.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>7.0%</td>
<td>5.7</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>4.7%</td>
<td>3.8</td>
</tr>
<tr>
<td>Diarrhea or Constipation</td>
<td>2</td>
<td>4.7%</td>
<td>3.8</td>
</tr>
<tr>
<td>Limb Edema</td>
<td>2</td>
<td>4.7%</td>
<td>3.8</td>
</tr>
<tr>
<td>Worsening hypertension</td>
<td>1</td>
<td>2.3%</td>
<td>1.9</td>
</tr>
<tr>
<td>Worsening Blood glucose</td>
<td>1</td>
<td>2.3%</td>
<td>1.9</td>
</tr>
</tbody>
</table>
by a survey performed six years after the publication of the ONTT study: 95% of neurologists had reduced the use of oral prednisone, with 65% and 53% stating high dose IV methylprednisolone was the most effective way to hasten visual recovery and to reduce future neurologic events of MS, respectively.13

Recent evidence supports the use of high dose oral corticosteroids as an alternative to IV therapy, as oral therapy is less expensive, more convenient and generally preferred by patients. However, Morrow et al demonstrated bioequivalence of 1250mg of oral prednisone and 1000mg of IV methylprednisolone. A survey study found MS specialists in Canada use both high dose oral and IV for relapse treatment. A 2009 Cochrane review found no significant differences between short term outcomes (≤ 6 weeks) of MS relapse treatment with oral vs. IV corticosteroids but did feel the review was limited by the small subject pool and methodological limitations.10. Our current study further supports the use of oral corticosteroids; not only did the majority of our subjects prefer oral corticosteroids, but also 94.3% were fully compliant, despite a high rate of side effects.

Compliance with oral medications is an issue that permeates all areas of medicine. Compliance is lowest in patients with psychiatric diseases such as depression and schizophrenia, with more than half of patients considered non-compliant. However, it is also an issue in other chronic illnesses with compliance in developed countries only at 50%. Compliance has also been poor in acute illnesses, requiring only a short course of treatment. For children with otitis media, compliance with antibiotics has been found to range from 18-95% and for adults discharged with a short course of medication from emergency departments, compliance ranges from 50-78%. Thus, our compliance rate of 94.3% is excellent and is not a deterrent to oral prednisone treatment.

There are many limitations to this study. To begin, the London MS clinic uses 1250mg oral prednisone per day for relapse treatment as the first line therapy; subjects who prefer IV therapy may have sought treatment elsewhere, such as with his/her primary care physician, walk in clinics or in the emergency department. Secondly, many of the subjects had received oral corticosteroids before and this may have biased the sample towards subjects who already tolerate or prefer oral administration of corticosteroids. Both of these limitations may have biased the sample towards MS patients who prefer oral administration prior to enrollment in the study. However, almost 2/3 of the cohort (35, 66.0%) had either not received corticosteroids or had only received IV formulations, in the past. Further, this study was based on self-reported compliance which can only be assumed to be fully accurate. Additionally, efficacy was not addressed in this study, only compliance and adverse events, and thus no comment can be made regarding the efficacy of oral corticosteroids for acute demyelinating events. However, other studies previously mentioned do address this issue.5,9 Finally, any subject who had a relapse severe enough to be hospitalized was not included, limiting the sample to mild or less disabling relapses.

Conclusions

There is little concern regarding adverse events and compliance with high doses of oral corticosteroids for the treatment of acute demyelinating events. However, should the patient be intolerant to the oral treatment, IV therapy can be considered as an alternative.

References