

Paroxetine vs pregabalin for the management of neuropathic pain in multiple sclerosis

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Received: August 15, 2013 Revised: June 12, 2014

Accepted: June 14, 2014

Published online: July 27, 2014

METHODS: A randomized, flexible-dose open-label 8-wk study involving 21 relapsing-remitting MS patients with MS-induced NPP was conducted to evaluate the effectiveness and tolerability of pregabalin versus paroxetine for pain management. The trial included a 3-wk dose titration phase followed by a 5-wk stable dose phase. Primary outcome measures included daily patient-reported pain intensity as measured using a 100 mm visual analogue scale (VAS_{pain}) and daily impact of pain on daily activities (VAS_{impact}). Hierarchical regression modeling was conducted on each outcome to determine if within person VAS trajectory for pain and impact differed across study groups, during 56 d follow-up.

RESULTS: Attrition rates were significantly greater ($P < 0.001$) in the paroxetine versus pregabalin study group (70% vs 18.2%, respectively). Average study duration between study groups also significantly differed ($P < 0.001$). Paroxetine participants completed an average of 27.3 d of treatment vs 49.5 d in the pregabalin group, with the majority of patients withdrawing due to adverse events. Due to the high attrition rates in the paroxetine study arm, the investigators stopped the study prior to achieving complete recruitment. As such, no significant differences between pregabalin and paroxetine study arms were noted for the primary outcome measures (VAS_{pain}, VAS_{impact}). Comparative assessment of baseline patient characteristics also revealed no significant differences between the study arms.

CONCLUSION: High attrition rates associated with paroxetine use suggest that it be used with caution for MS-induced NPP. Efficacy outcomes could not be assessed due to attrition.

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Key words: Multiple sclerosis; Neuropathic pain; Paroxetine; Pregabalin; Clinical trial

Abstract

AIM: To compare the effectiveness and tolerability of paroxetine vs pregabalin for the management of multiple sclerosis (MS)-induced neuropathic pain (NPP).

Core tip: The high attrition rates identified in the paroxetine study arm suggest that it be used with caution for multiple sclerosis (MS)-induced neuropathic pain (NPP). Although analysis of the primary endpoint measures revealed no significant differences, there was a trend toward marked improvement for visual analogue scale and daily impact of pain on daily activities in favor of pregabalin. However, due to the premature study cessation, definitive confirmation of pregabalin's enhanced efficacy was not possible. These results reinforce the recognized challenges clinicians encounter in drug selection for MS-induced NPP. Due to the lack of well-designed controlled NPP trials in this population, effective and well-tolerated treatment selection poses a significant clinical challenge.

Turcotte DA, Doupe M, Torabi M, Gomori AJ, Ethans K, Esfahani F, Galloway K, Namaka MP. Paroxetine vs pregabalin for the management of neuropathic pain in multiple sclerosis. *World J Anesthesiol* 2014; 3(2): 181-188 Available from: URL: <http://www.wjgnet.com/2218-6182/full/v3/i2/181.htm> DOI: <http://dx.doi.org/10.5313/wja.v3.i2.181>

INTRODUCTION

Multiple sclerosis (MS) is a chronic, neurodegenerative disease that affects over two million people world-wide^[1]. Pain is recognized as one of the most significant MS-induced symptoms. It has been reported that up to 80% of MS patients experience some form of chronic pain^[2-5]. MS-induced neuropathic pain (NPP) is a chronic pain syndrome caused by damage to the nerve fibers involved in the synaptic transmission of pain. Hallmark clinical symptoms include sensory abnormalities such as: numbness, burning, feeling of pins and needles, tingling sensations and shock-like pain^[6,7].

At present, there is no cure for MS-induced NPP. Henceforth, treatment goals are focused primarily on reducing pain to a more tolerable level. Patients with NPP often suffer other co-morbidities such as mood and sleep disorders^[8,9]. Clinicians are therefore faced with the additional challenge of selecting a therapeutic option capable of managing all these domains associated with chronic pain. For example, antidepressant medications possess a distinct advantage of having analgesic and antidepressant/sedative properties that assist with both pain, mood and sleep issues. As such, tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, are recommended as first-line agents for NPP^[10]. TCAs elicit their analgesia through the pre-synaptic reuptake inhibition of serotonin (5-HT) and norepinephrine (NE), thereby enhancing descending pain modulating pathways^[11]. In addition, TCAs have also been shown to exhibit sodium and calcium channel blockade, resulting in decreased neuronal hyperexcitability^[11]. Despite documented effectiveness in various NPP conditions, the usefulness of TCAs in MS is often limited due to poor tolerability^[11]. MS pa-

tients often suffer a variety of disease-induced symptoms that include: dizziness, ataxia, bladder/bowel retention, drowsiness and fatigue. These underlying disease induced symptoms can all be potentially intensified by the addition of a TCA to their medication regimen. As such, in many cases, it is difficult to attain therapeutic dosages to successfully control their pain.

Selective serotonin reuptake inhibitors (SSRIs) are antidepressant medications that may be better tolerated in individuals with MS due, in part, to the lack of anticholinergic effects. SSRIs selectively block the pre-synaptic reuptake of 5-HT, resulting in an accumulation of 5-HT in synapses involved in the transmission of pain. As such, analogous to TCAs, SSRIs are suggested to have an analgesic role via potentiating the descending pain inhibitory mechanisms^[12]. Interestingly, a recent animal model evaluating the analgesic effects of the SSRI paroxetine suggests an additional mechanistic link to produce analgesia *via* opioid systems^[13]. Although limited, there is some evidence supporting the analgesic efficacy of SSRIs in NPP. In two randomized, placebo controlled trials, citalopram^[14] ($n = 17$) and paroxetine^[15] ($n = 20$) were both found to be effective at reducing pain intensity associated with diabetic peripheral neuropathy (DPN) when comparatively assessed against placebo. Citalopram, dosed at 40 mg daily, was found to significantly reduce self-reported pain intensity ($P = 0.007$), and was well-tolerated with two individuals receiving active treatment withdrawing early due to adverse events (nausea and vomiting, gastric upset)^[14]. Paroxetine evaluated for DPN in a placebo-controlled cross-over design at a dosage of 40 mg daily was found to be significantly better at reducing self-reported pain intensity than placebo ($P = 0.012$)^[15]. No individuals receiving paroxetine in this trial withdrew early. Although, paroxetine has been evaluated for depression in MS^[16], to the best of our knowledge, it has not been evaluated for MS-induced NPP.

In addition to antidepressants, several other first-line agents have been used in the treatment of NPP, including pregabalin^[10]. Pregabalin is an anticonvulsant medication thought to elicit analgesic effects through interaction with the $\alpha 2\delta$ subunit of N-type voltage-dependent Ca^{2+} channels, ultimately reducing overall neuronal excitability^[17]. Several large controlled trials have demonstrated consistent efficacy results for use in post-herpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN)^[18-20]. Formal evaluation of pregabalin for use in MS-induced NPP, however, is limited. One open-label pilot study evaluating the effect of pregabalin (mean dosage 154 mg daily) on paroxysmal painful symptoms in MS ($n = 16$) found it to be both efficacious at reducing pain from time 0 to one month follow-up ($P < 0.05$) and well-tolerated^[21].

At present, few drugs are approved specifically for MS-induced NPP^[22]. In fact, MS-induced NPP is often managed by the off label use of medications. Hence, outcome measures of efficacy and tolerability in clinical trials focused on NPP resulting from diabetes, herpes zoster or injury, are often employed to drive therapeutic decision-

Table 1 Study eligibility requirements

Inclusion criteria	Exclusion criteria
Males and females 18-65 years old	Breastfeeding
Clinically definite RRMS	History of alcohol or other substance abuse
EDSS \leq 6.5	Significant hepatic/renal insufficiency
VAS score for NPP symptoms $>$ 5	Significant cardiac disease (CHF, arrhythmia); hypertension
Pain present for at least 3 mo	Hypersensitivity/allergy to study medications or their derivatives
Negative serum pregnancy test	No current therapeutic duplications No history of psychotic/non-psychotic emotional disorders

Inclusion and exclusion criteria for enrolment in the study are noted above. RRMS: Relapsing-remitting multiple sclerosis; EDSS: Expanded Disability Status Scale; NPP: Neuropathic pain; VAS: Visual analogue scale; CHF: Congestive heart failure.

making in the MS population. Due to the lack of focused research specifically evaluating therapies for MS-induced NPP, we have undertaken a study aimed to evaluate the efficacy and tolerability of paroxetine and pregabalin for the management of NPP in individuals with relapsing-remitting MS (RRMS). We hypothesize that pregabalin would significantly reduce daily absolute pain when compared to paroxetine with similar tolerability. To our knowledge, this is the first study to formally compare these agents for the management of NPP in RRMS.

MATERIALS AND METHODS

A randomized, open-label, parallel pilot study was conducted at the MS clinic of the Health Sciences Centre in Winnipeg, Manitoba, Canada over a 4-year-period. Ethical approval for this study was obtained by the Biomedical Research Ethics Board of the University of Manitoba. Study procedures adhered to practices outlined in Good Clinical Practice Guidelines. Based on stringent enrolment criteria, eligible patients providing written informed consent were enrolled for participation into the trial. Eligibility inclusion criteria comprised: (1) males and females between the ages of 18-65 years old, (2) clinically definite RRMS, as defined by the McDonald Criteria^[23], (3) expanded Disability Status Scale (EDSS) score of $<$ 6.0 (*i.e.*, not restricted to a wheelchair)^[24], (4) no concurrent MS relapse at time of enrolment, and (5) Visual Analogue Scale (VAS) score for NPP symptoms \geq 5 with pain symptoms present for at least 3 mo prior to enrolment. Eligibility exclusion criteria comprised: (1) pregnancy or breastfeeding, or immediate conception plans; (2) known history of alcohol and/or substance abuse; (3) history of non-psychotic emotional disorders; (4) significant hepatic and/or renal insufficiency that would require dose adjustments of study medications; (5) significant cardiovascular disease (congestive heart failure, cardiac rhythm abnormalities) and/or uncontrolled hypertension (systolic blood pressure \geq 140 mmHg, diastolic blood pressure \geq 90 mmHg); (6) documented hypersensitivity to par-

oxetine or pregabalin or any of their derivatives; and (7) current medications with potential significant interactions with study meds (as determined by clinical pharmacist). In addition, patients were allowed to remain on current pain medications provided medications have been at stable dosages for at least 6 mo and must not interact with study medications. Please refer to Table 1 for a complete summary list of all the inclusion and exclusion criteria.

All eligible, consenting patients were randomized to receive treatment with either paroxetine or pregabalin. Randomization assignments, completed by an individual independent of the study, were generated using pre-programmed computer software (Microsoft Excel®) employing a random permuted blocks approach^[25]. To minimize the ability to predict subsequent treatment assignments, it was selected to also randomize the block sizes, varying them as either 2 or 4 patients per block. Results of the randomization generation were placed within opaque envelopes numbered sequentially. After all pre-screening and consenting procedures were done, the subsequent treatment assignment envelope was opened and randomization result provided.

Once randomized to drug treatment, patients completed a physician-conducted baseline screening (Baseline Assessment), during which they underwent baseline physical and neurological examinations. Additionally, patients were provided with a daily pain diary (DPD), required for daily self-completion to monitor the intensity and impact of pain. Patients were instructed to record their daily pain score upon waking each morning in the DPD provided to them. The DPD was comprised of a vertical VAS scale of 0 mm (no pain) to 100 mm (worst pain imaginable) and patients were required to record their daily pain score (intensity) over the previous 24 h (VAS_{pain}). In addition, the DPD contained a second identical vertical VAS scale to evaluate the impact of daily pain on their daily activities (VAS_{impact}), anchored this time with 0 mm (no effect) to 100 mm (incapacitating). At the end of the baseline assessment, patients were provided with dosing instructions for the subsequent three-week "titration period".

Dosing instructions were dependent on treatment assignment, and included three possible weekly increases. Patients were contacted by phone prior to the initiation of the subsequent dosage step. If patients were experiencing significant adverse events or \geq 50% pain relief at the current dose, in collaboration with the patient, it was within the clinician's discretion to halt dosage increases and instruct individuals accordingly. Please refer to Table 2 for a summary of the suggested dosage schedule.

Patients were required to return to the clinic for an adverse event assessment at the end of the "titration phase" (Post-Titration Assessment). At this time, patients completed a standardized "Adverse Event Checklist" containing a word-list of possible side effects to document any current or previously experienced symptoms since beginning the study. To minimize prompting, passive collection of adverse events was facilitated through the inclusion of adverse event descriptors of known association to the study drugs and those of less common

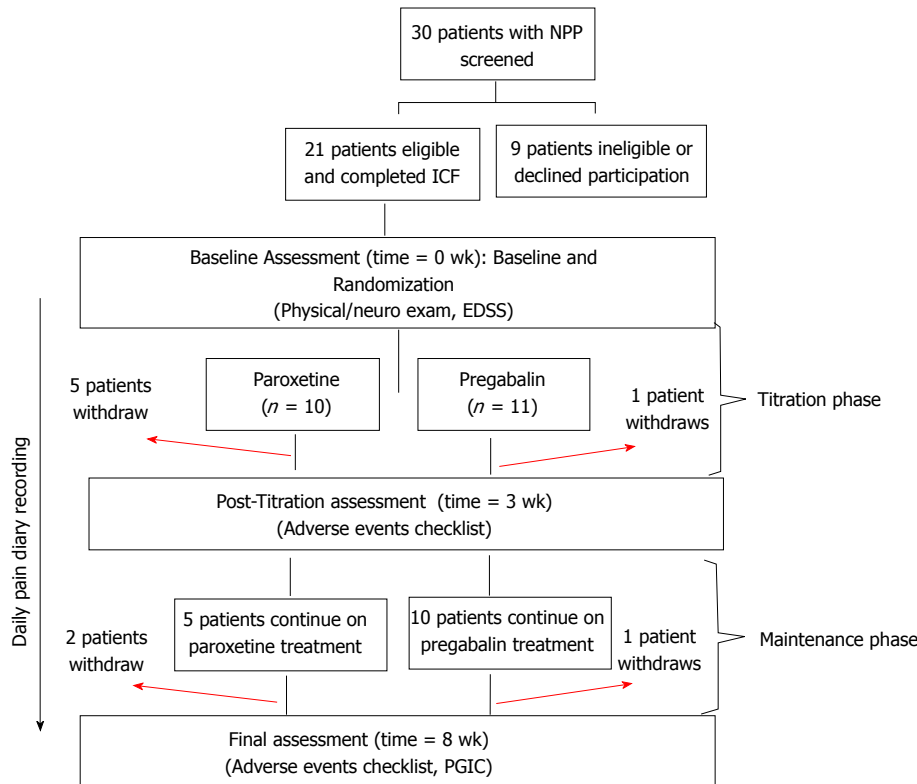


Figure 1 Study schedule summary. Patient screening outcomes and visit schedule summaries are provided. Bracketed information on specified “Assessment” lines indicates evaluations conducted at each visit. NPP: Neuropathic pain; ICF: Informed consent form; EDSS: Expanded disability status scale; PGIC: Patient rated global Impression of change.

Table 2 Paroxetine/pregabalin flexible-dose titration schedule

Schedule	Dosage	
	Paroxetine	Pregabalin
Day 1	20 mg once daily	75 mg twice daily
Day 8	40 mg once daily	150 mg twice daily
Day 15	50 mg once daily	300 mg twice daily

Flexible-dose titration schedule for each group is presented. Assuming therapy was well-tolerated patients were instructed to increase dosages as indicated above. If, however, at any point patients experienced intolerable side effects they were instructed to contact study investigators for tailored dosing instructions.

or unknown association, in random order. At the end of the post-titration assessment the current dose that the patient was able to attain by the end of the titration phase was entered as their stable dose for the subsequent 5-wk “maintenance phase”. DPD recording continued over the 5-wk maintenance phase. At the end of the maintenance phase patients returned to clinic for one final visit (Final Assessment) where they completed the same Adverse Event Checklist. Additionally at this time, patients were required to complete the Patient-Rated Global Impression of Change (PGIC). This tool is used to evaluate the patient’s perception of their assigned treatment on their pain symptoms. Patients were asked to rate their overall pain at this time point in comparison to their pain at the baseline assessment. Selection options included: (1) very much improved; (2) much improved; (3) minimally improved; (4) no change; (5) minimally worse; (6) much worse; and (7) very much worse. The PGIC is well-validated for assessing patient perception on clinical treat-

ment outcomes^[26]. Please refer to Figure 1 for a summary of the clinical trial timeline.

Statistical analysis

Baseline patient covariates were compared for group differences using either an independent t test for continuous measures or a chi-squared test for the categorical measure (patient sex). Daily VAS_{pain} and VAS_{impact} data exist at two levels (time and person), therefore a hierarchical model was used to assess the rate of within person change in these outcomes, differences in these outcomes across study groups collapsed across all times, and most importantly, group × time interactions to determine if the rate of change in VAS_{pain} and VAS_{impact} differed significantly by group^[27]. All data analyses were conducted using R Software (2013)^[28].

Sample size calculation

The required sample size in each treatment group was calculated based on the procedure outlined by Diggle *et al.*^[29]. It was assumed that the treatment allocation and baseline differences accounted for at least 13% of the total variation in daily VAS, which corresponds to a medium effect size defined by Cohen^[30]. As well, there were 56 repeated measures for each subject with alpha set at 0.05 and the power was set at 0.8. Predicted drop-out was determined from results of previous clinical trials (pregabalin average 15.5%^[31,32], paroxetine 19%^[33]). The drop-out rates were accounted for using the method described by Sakpal (2010)^[34]. Therefore, it was found that there should be a sample size of approximately 24 subjects would be required (12 in each study arm).

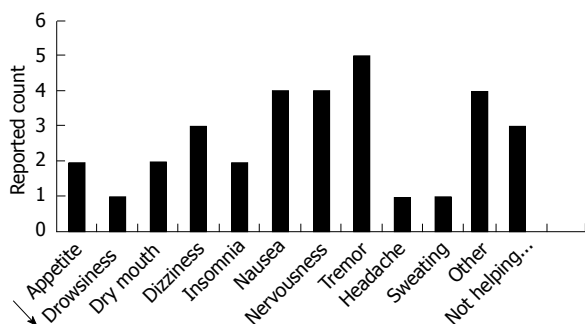


Figure 2 Patient-reported reasons for study attrition: paroxetine arm. Patient-reported reasons for attrition are presented ($n = 7$). Patients were permitted to cite multiple reasons for treatment discontinuation. "Other" included complaints of feeling "shaky", "caffeinated", "jittery" and "anxious".

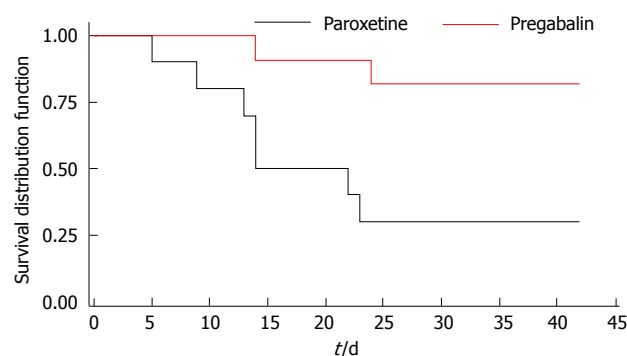


Figure 3 Attrition by study group. Attrition rates (shown in the format of survival distribution by study day) for each group (paroxetine and pregabalin) are presented. The average study duration (days) for paroxetine = 27.3 and for pregabalin = 49.5.

RESULTS

Collectively, 30 patients were screened for enrolment into the trial, prior to early closure of the study due to high drop-out rates. Of these patients, 7 were found to be ineligible based on inclusion/exclusion criteria (Table 1) and two were eligible but elected not to participate. Ultimately, 21 patients consented and were enrolled for participation in the study (10 randomized to paroxetine and 11 to pregabalin). No significant differences were noted between the groups on any of the baseline cohort characteristics collected. This information is summarized in Table 3.

Significant differences ($P < 0.001$) in attrition rates were identified between the two study groups that favored the pregabalin treatment arm. Specifically, in the pregabalin study arm, a total of 2 patients (18.2%) did not complete the entire 8-wk duration of the study. Conversely, assessment of the paroxetine study arm identified 7 patients (70%) that were not able to complete the study. The average percentage of maximum dosage was compared by study arm and did not differ significantly. This information is summarized in Table 3. Both patients who withdrew early in the pregabalin study arm did so as a result of intolerable sedation and dizziness. Attrition reasons for the paroxetine arm are summarized in Figure 2, with the most commonly reported attrition reasons being tremor, nausea and feelings of nervousness. Figure 3 illustrates drop-out as a survival plot. In comparing the average study duration (days) by study group, paroxetine was found to have a significantly lower mean than pregabalin (27.3 d *vs* 49.5 d, respectively, $P < 0.01$). This information is presented in Table 4.

Primary outcome measures were compared between the groups, with univariate modeling for VAS_{pain} and VAS_{impact} demonstrating all non-significant findings. These results are presented in Table 5. Comparative assessment of 8 wk trial data involving patient-perceived treatment effect, (evaluated using the PGIC), revealed no statistically significant differences between treatment arms.

DISCUSSION

Individuals with MS can be plagued by many unique

disease-induced symptoms not commonly seen in other NPP conditions, including: ataxia, dizziness, cognitive impairment, imbalance, bladder/bowel dysfunction and visual disturbances. Many of the current first-line treatment recommendations from general NPP guidelines have the potential to induce drug-related adverse effects that can mimic and worsen MS disease symptoms. As such, tolerability limitations must be considered when translating general NPP guideline recommendations to MS-induced NPP clinical management. This is made evident by the outcomes of the current trial, which indicated a significantly high attrition rate in those patients treated with paroxetine versus pregabalin ($P < 0.001$). The results of our study in this specific patient population contradicts the favorable tolerability of paroxetine in reported in other clinical pain trials, such as burning mouth syndrome^[33] and DPN^[15]. Our results suggest that due to other underlying disease induced symptoms commonly associated with MS, paroxetine may not be the most suitable choice for this patient population. Furthermore, the combination of stringent enrollment criteria and recognized high attrition rates hindered patient enrollment for this study. As result, the reduced sample size prevented optimal assessment of the proposed primary study aims developed to assess efficacy.

Irrespective of these challenges, the primary outcome measures (VAS_{pain} and VAS_{impact}) were compared univariately revealing no significant difference between groups. In addition, patient-perceived treatment benefit—as determined by the PGIC at the Final Assessment—did not differ significantly between the groups, reinforcing the equivocal results of this trial. Due to the high attrition rate in the paroxetine study arm, comparison of primary outcomes between the groups is compromised due to small numbers of patients remaining after the mid-point of the study. As such, comparison results must be interpreted cautiously as the ability to detect any potential differences is greatly restricted.

In addition to the high attrition and resultant reduced study power, our study is not without further limitations that may impact interpretation of results. Our study was developed as an open-label design. As a result of patient's

Table 3 Study patient characteristics

	Total	Paroxetine	Pregabalin	P value
<i>n</i>	22	10	11	N/A
Demographic				
Age: mean (SD)	45.7(12.49)	43.1(12.85)	48.1(12.28)	0.374
Sex: % female	81	90	72.7	NS
Clinical				
EDSS: mean (SD)	2.3(1.44)	2.6(1.29)	1.9(1.57)	0.34
Baseline pain: mean (SD)	71.5(10.66)	68.3(10.11)	74.7(10.73)	0.19
Duration of pain (mo): mean (SD)	25.75(19.77)	22.5(19.72)	29(20.31)	0.48
Time since MS diagnosis (yr): mean (SD)	9.39(8.63)	7.8(8.79)	11.38(8.57)	0.4
Analysis				
% withdrawal from study	40.9	70	18.2	< 0.001
Average final daily dose (mg) attained (% of maximum possible)	N/A	31 (62)	422.7 (70.5)	N/A

Baseline characteristics—categorized as either “demographic” or “clinical” are presented collectively for all patients combined ($n = 22$) as well as individually for paroxetine ($n = 10$) and pregabalin ($n = 11$) patient groupings. Where appropriate, mean and SD are provided. “Analysis” subheading provides information on the number of patients who withdrew prematurely from the study (“% withdrawal from study”) by group as well as the final average daily dose attained in each group. *P* values have been provided to estimate equivalence of groups. EDSS: Expanded disability status scale; NS: No significant; N/A: Not available.

Table 4 Average study duration (d) by study group

Average study duration by group (d)					
	<i>n</i>	Mean days in study	SD	Range of values	
				Lower	Upper
Paroxetine	10	27.3	21.6	5	58
Pregabalin	11	49.5	15.7	14	63

The mean duration of participation in the study by group is presented, with associated SD and range; Independent *t* test between groups, $P < 0.01$.

awareness of active treatment, psychosomatic contributions may have contributed to any primary outcome effects. Although blinding and controlling for bias through inclusion of a placebo arm would have undoubtedly strengthened the power of the study ethical restraints prevented study blinding as neither of the comparative agents selected for the study had approved indication from Health Canada for MS-induced NPP. As a result, this aspect of study design was not incorporated to ensure complete transparency in that the enrolled patients were fully informed of the use of an off-label medication to manage their pain.

MS presents an especially challenging disease to effectively manage NPP. This in part is not only due to confounding disease-induced symptoms, but also due to the polypharmacy that is often observed in this population. Individuals with MS are often on multiple medications to manage the multifaceted nature of their primary disease. As such, NPP treatment options are further limited due to potential drug interactions and/or therapeutic class duplication issues. These unique treatment considerations make simply applying current general NPP guidelines directly to MS care inappropriate. Most guidelines for NPP are created based on large-scale studies in various other NPP conditions, such as DPN and post-herpetic neuralgia. Although, mechanistically, it is likely that current first-line agents for NPP would target the underlying pain mechanisms of MS-induced NPP, the inability to tolerate

Table 5 Univariate comparison results: VAS_{pain} and VAS_{impact}

	VAS _{pain}	VAS _{impact}
	RR	RR
Group	8.7270	3.4270
Day	0.5036	0.5065
Group × day	0.1513	0.1918

Univariate comparison results are presented on data from study participants completing the study. No significant findings were noted between comparisons. RR: Relative risk.

these medications and achieve therapeutic dosages can be significantly hindered. The only way to appropriately apply guideline recommendations to this unique patient population is by first validating their efficacy and tolerability in these patients in accordance with a randomized, controlled setting. Unfortunately, data from randomized clinical trials (RCTs) for MS-induced NPP is significantly lacking. Until the need for well-designed RCTs in MS-induced NPP is met, clinicians managing pain in this patient population must first consider tolerability issues of therapy rather than relying solely on the general NPP guidelines that encompass all patients with NPP irrespective of origin. In order to optimize treatment success, careful review of patient-reported disease-induced symptoms must be completed to determine which medications being considered for NPP would have the lowest likelihood of aggravating these underlying complaints. Additionally, a thorough review of concomitant medications would also be of benefit. Once an appropriate treatment is selected, a conservative dosage titration schedule should be followed in order to minimize adverse events and prevent drug interactions with existing therapy. Frequent follow-up to facilitate communication between clinician and patient should be established to ensure that realistic treatment goals as well as realistic timelines for these outcomes are met.

In summary, due to the high attrition rates observed

in this study resulting in premature closure, primary pain outcomes could not be appropriately assessed. Paroxetine, which has been found to be well-tolerated and effective for other chronic pain conditions, has been found poorly tolerated in this study. These results suggest that paroxetine should be used cautiously in those with MS-induced NPP. The unique tolerability issues observed in individuals with MS-induced NPP make the application of general therapeutic NPP guidelines inappropriate for many in this population, without consideration of additional disease-induced factors that may affect drug safety. Available guidelines are helpful tools for clinicians, however cannot be considered absolute due to unique needs of individuals in an MS population. Expert clinical judgement appropriately considering the therapeutic requirements of this population along with evidence-based data from other NPP states is therefore required, as it is unlikely that evidence-based guidelines specific to MS-induced NPP will be developed due to the lack of RCTs in this population. Collaborative communication between clinicians specialized in both MS care and pain management would ultimately improve therapeutic selection, implementation and follow-up resulting in improved tolerability and efficacy outcomes.

COMMENTS

Background

Neuropathic pain is a painful condition that can result from a number of different pathophysiological and disease-induced causes, and can be significantly challenging to control for many individuals. The majority of neuropathic pain management guidelines available to guide patient care are based upon larger scale pharmacotherapeutics trials in the more prevalent neuropathic pain conditions, including diabetic peripheral neuropathy, post-herpetic neuralgia and trigeminal neuralgia. Multiple sclerosis (MS) is a chronic, progressive neurological condition that can frequently result in the development of neuropathic pain. Due to the often complicated presentation of co-morbid disease-induced symptoms, treatment of neuropathic pain in individuals with MS can be challenging due to poor tolerability of first-line agents. Clinical trials specific to the MS population with neuropathic pain are rare, however they are essential in order to better understand safety and efficacy in this unique patient population. Both the antidepressant and antiepileptic classes of medication are used as first-line agents for many neuropathic pain conditions, however their efficacy and tolerability in individuals with MS-induced neuropathic pain are not well-studied.

Research frontiers

Paroxetine is a selective serotonin reuptake inhibitor antidepressant. Antidepressants are currently touted as first-line agents for the management of painful neuropathies not only based on their analgesic effects but also their effect on co-morbid mood and sleep issues often associated with chronic pain. Pregabalin is an antiepileptic and antineuralgic medication that is relatively new to the market and is also recommended as a first-line agent for the management of neuropathic pain.

Innovations and breakthroughs

Most clinical trials evaluating the efficacy and tolerability of specific medications for effects in various neuropathic pain conditions look at the effect of a specific agent against a placebo comparator. Although this is important to establish treatment effect, it does not allow us to differentiate between the various first-line agents. Additionally, very few clinical trials evaluating therapy for neuropathic pain in individuals with MS have been conducted. In an attempt to provide some initial information on the management of neuropathic pain in this patient population the authors have conducted a head-to-head clinical trial comparing paroxetine vs pregabalin to assess both efficacy and tolerability in this understudied patient group.

Applications

The results of this study provide us initial insight regarding the use of "first-line"

agents in the management of neuropathic pain. The high rate of intolerability in the paroxetine treatment arm was surprising based on literature use in other patient populations. This reinforces to clinicians that individuals with MS present unique and complex clinical cases that may limit the use of agents considered "first-line" in other painful neuropathies.

Terminology

MS-induced neuropathic pain (NPP) is a chronic pain syndrome caused by damage to the nerve fibers involved in the synaptic transmission of pain. Pregabalin is an anticonvulsant medication thought to elicit analgesic effects through interaction with the $\alpha 2\delta$ subunit of N-type voltage-dependent Ca^{2+} channels, ultimately reducing overall neuronal excitability. Paroxetine is a selective serotonin reuptake inhibitor that selectively blocks the pre-synaptic reuptake of 5-HT, resulting in an accumulation of 5-HT in synapses involved in the transmission of pain.

Peer review

The primary aim was to compare the analgesia effect and improve of quality of daily life quality by the administration of Paroxetine and Pregabalin in neuropathic pain patients with MS. The study was well designed and written given the consideration of various factors confounding in this particular patients population.

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