Spasticity increases during pregabalin withdrawal

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Abstract

Primary objective: To determine whether pregabalin produces long-term spasticity reduction in subjects previously identified as responding in short-term trials.

Design, subjects and setting: Prospective service evaluation of patients taking pregabalin for spasticity management for at least 1 year through a tertiary referral rehabilitation clinic. A graduated pregabalin withdrawal was undertaken as part of routine clinical management.

Method: Twelve of 19 potential subjects agreed to participate. The primary outcome measures were visual analogue pain and spasticity scores at lowest dose of pregabalin compared to baseline and their choice to resume pregabalin therapy.

Results: Mean pre-withdrawal pregabalin dosage was 386 mg/day, decreasing to 70 mg/day at mean lowest dosage. Median subjective spasticity scores increased from 4 at baseline to 6 at lowest dose ($p < 0.01$) without a significant increase in median pain scores. Two patients with epilepsy, whose other anti-convulsants were not altered, had seizures. Following the evaluation, five subjects chose to return to the original dose, five recommenced pregabalin at a lower dose and two subjects no longer required the drug.

Conclusion: Pregabalin withdrawal resulted in self-reports of increased spasticity without a concomitant increase in pain, with 91% choosing to continue pregabalin at the conclusion of the evaluation.

Keywords: Spasticity, acquired brain injury, pregabalin, pain, epilepsy

Introduction

Spasticity is defined as a velocity dependent increase in muscle tone as one part of the upper motor neurone lesion \cite{1}, a characteristic that is often associated with disordered sensorimotor control \cite{2}. Severe spasticity can adversely impact upon activities of daily living \cite{3}, the successful management of which often requires a multimodal approach with regular evaluation of treatment efficacy \cite{4}. Modalities to treat spasticity include physical therapies \cite{4}, medications \cite{5}, neurotoxic agent injections \cite{6–8}, insertion of intrathecal baclofen pumps \cite{9, 10} and surgical interventions such as the SPLATT procedure, soft tissue or tendon releases \cite{11}.

Oral medication is introduced when spasticity cannot be controlled via non-pharmacological methods and where pain, hygiene and self-care are problematic. There are few medicines licensed for spasticity in the UK (baclofen, tizanidine, dantrolene and diazepam) among which side-effects including sedation, cognitive blunting, weakness and hepatotoxicity \cite{5} are well recognized. While gabapentin, a gamma-amino butyric acid analogue, is licensed for the treatment of post-herpetic neuralgia and partial epileptic seizures \cite{12}, it is prescribed and shows

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effectiveness in controlling spasticity [13–15]. It is recommended as a first-line agent in the treatment of spasticity for multiple sclerosis in the current UK National Clinical Guidelines [16].

Pregabalin is structurally similar to gabapentin but with the advantage of better and more consistent bioavailability [17]. Pregabalin has been licensed since 2004 for treatment of neuropathic pain [18], adjunctive therapy for partial epileptic seizures [19] and generalized anxiety disorder [20]. While anecdotal reports suggest that pregabalin may be effective in the management of spasticity, there is little objective evidence. However, a retrospective case series review of 22 patients using pregabalin as monotherapy for spasticity reported that 12 patients exhibited a definite reduction in symptoms of spasticity [21].

It is common rehabilitation medicine practice to undertake a trial reduction or withdrawal of medication that is prescribed for chronic conditions, such as pain, spasticity, bladder instability and emotional lability to see if the medication remains necessary. This study took the opportunity to systematically document changes in user’s spasticity and pain and their overall impression of this medication, to inform design of any future randomized controlled trial. This study design, that is, withdrawal of a study medication in known responders, has been used in two trials of Sativex cannabis spray for spasticity, utilizing patient self-reported spasticity severity scores as a primary outcome measure [22–24].

Methods

Approval for this service evaluation was obtained from the local institutional human research and development committee. Thirty-eight patients were identified from the clinical database of one of the authors (SGBK) as having been prescribed open-label pregabalin as part of their spasticity management after standard spasticity medications had failed to control their symptoms. Of these patients, five were medically unstable, four had ceased pregabalin, two had only recently been prescribed the medication and eight were uncontactable or otherwise unable to communicate. The remaining 19 subjects were approached to participate in the study.

For participants, each was assessed on a battery of measures (outlined below) while taking their usual pregabalin dose. At initial assessment, each patient’s subjective report of spasticity and pain severity, side-effects and preference for pregabalin or previous agents were documented. Patients muscle tone was documented using the Modified Ashworth Scale (MAS) [25], a 5-point Global Assessment of Benefit (GAB) scale [8] and the spasticity related sections of the Multiple Sclerosis Severity Scale (MSSS-88) [26]. The initial pregabalin dose was reduced by 25% every third day, until the individual reached their lowest tolerated dose or ceased pregabalin completely (occurring on day 13). The initial assessment regime was then repeated on the final day of the service evaluation, whereupon patients experiencing increased spasticity or pain were given the option to recommence pregabalin at their preferred dose. In addition, patients also recorded daily subjective assessments of spasticity and pain on a visual analogue scale (rated 0 = absence of the feature and 10 = the worst state imaginable) rounded to the nearest integer.

The final VAS and GAB score at lowest pregabalin dose were compared relative to the third baseline day using the Wilcoxon Matched-Pairs Signed-Ranks Test, with significance set at $p < 0.05$.

Results

Twelve of the 19 patients consented to undertake the graduated withdrawal protocol. Participants were nine males and three females with a median age of 51 years (IQR = 39). Two subjects had a history of multiple sclerosis, five an adult-onset acquired brain injury, two a spinal cord injury and three cerebral palsy. Patients had been taking pregabalin for a median 18 (IQR = 12) months, with a median dose of 300 mg/day (IQR = 130 mg). Five patients were receiving inter-current anti-spasticity medication: four were taking a single agent (two tizanidine, one baclofen and one intrathecal baclofen) while one person had three agents (baclofen, diazepam and botulinum toxin A 5 weeks pre-trial). Doses of these medications remained stable throughout the trial.

Spasticity VAS scores increased significantly during withdrawal (see Table I), but there was no significant change in Ashworth scores, pain scores or MSSS-88 sub-scores for spasms or effect on mobility and ADLs.

Median spasticity VAS score increased significantly as pregabalin was withdrawn, from 4 (IQR = 4.0) on day 3 of baseline to 6 (IQR = 4.0) on the lowest achieved dose ($p < 0.01$). GAB decreased significantly relative to baseline ($p = 0.02$), with a median reduction of −1.0 (IQR = 1.3). Nine of the 12 subjects (75%) reported a worsening of spasticity symptoms accompanying reduced pregabalin dosage (in terms of GAB and spasticity VAS), with two feeling unchanged and one feeling better off the medication. Group median pain scores remained at 0 across this interval ($p > 0.05$), although pain levels increased by 1 VAS point or greater for three patients. Two patients with well controlled epilepsy, whose other anti-convulsants were not altered.
during the trial, had seizures on complete cessation of pregabalin.

Subjects were divided into two groups based on their global assessment of benefit score. Subjects reporting no change in GAB with pregabalin reduction all completed the dose withdrawal trial and reported lower spasticity and pain scores across the trial (shown in Figure 1). Two ceased pregabalin and the third continued on 75 mg per day, representing a 95% dose reduction in this group. Of interest, one patient ceasing pregabalin was on three other anti-spasticity medications at the time of the trial and was reported to be more alert by carers. This person recommenced pregabalin 1 month after cessation due to an increase in spasticity-associated pain.

Conversely, subjects reporting lower GAB scores across the trial had higher spasticity and pain scores at commencement, with increases in spasticity scores more evident than in pain scores across the trial. Six patients in this group did not achieve complete withdrawal, requesting a return to their original dose after reaching a minimum 50% reduction in dose. All six of these patients returned to their starting pregabalin dose. The three patients who reported lower GAB but managed to complete the withdrawal trial recommenced pregabalin with a mean reduction of 180 mg per day (35%).

### Discussion

This open-label prospective service evaluation of 12 patients taking pregabalin for spasticity aimed to clarify if subjects continued to experience symptomatic benefit after more than 12 months on treatment. Overall, group VAS and GAB data suggested that pregabalin withdrawal resulted in statistically and clinically significant increases in spasticity rather than pain.

#### Table 1. Spasticity and pain raw scores.

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose</th>
<th>100%</th>
<th>100%</th>
<th>100%</th>
<th>75%</th>
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</tbody>
</table>

| Pain VAS | S1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|          | S2 | 2 | 5 | 5 | 4 | 4 | 4 | 5 |
|          | S3 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
|          | S4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|          | S5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|          | S6 | 5 | 5 | 6 | 6 | 6 | 6 | 8 | 8 | 8 | 10 | 10 |
|          | S7 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 1 | 1 | 1 | 0 | 0 |
|          | S8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|          | S9 | 1 | 3 | 1 | 5 | 5 | 5 | 4 | 4 | 6 |
|          | S10| 6 | 6 | 7 | 6 | 6 | 7 | 9 | 8 | 9 | 8 | 8 | 9 | 9 |
|          | S11| 5 | 6 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 6 |

S1– S11 denotes subject numbers. Dose refers to percentage of starting dose.
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than pain. The spasticity changes seen on VAS and GAB were not evident on the more formal, traditional measures such as the MAS. The lack of sensitivity of the MAS in this study may be due to too short a withdrawal period to allow group MAS changes or that the anti-spasticity effect of pregabalin has too small an effect size to show category change on a scale such as the MAS. Answering these questions represents an opportunity to explore in designing future intervention studies.

While the group reported significant spasticity increases with reduced pregabalin, three subjects did not report any short-term deterioration of spasticity in response to pregabalin withdrawal and reduced their pregabalin dose by 95% at the conclusion of the trial. One of this group recommenced pregabalin 1 month later. This groups reporting of change in spasticity over the trial differed markedly from the other nine participants who experienced a rapid increase in spasticity and, to a lesser extent, pain. Subjects with the greatest spasticity and pain increases did not tolerate pregabalin cessation. However, a third of the group were able to complete the trial and recommenced pregabalin at lower doses. In combination, these findings confirmed that the great majority of this highly selected group continued to report long-term efficacy of pregabalin for controlling their spasticity.

There was an overall reduction in pregabalin dosage across the participants following the completion of the trial of 38%. This finding supports the usefulness of a closely monitored graduated withdrawal protocol for medications that are administered for chronic disabling conditions for both the patient and the payor within the health system. Of concern, however, two known epileptic patients in this study had seizures despite remaining on their other regular anti-convulsants. The graduated withdrawal approach was adopted to minimize the risk of such an occurrence. The graduated withdrawal over 2 weeks was felt to be clinically achievable as well as safe, particularly in the light of a pregabalin neurogenic pain study that employed a periodic sudden cessation of open label treatment [27]. However, the occurrence of seizures in the current study suggests that withdrawal trials of pregabalin in spasticity may need to be implemented in a more gradual fashion in people with a history of epilepsy.

There are a number of limitations to this study. The study was open-label and it is impossible to rule out the influence of psychological factors in patients’ self-reporting, particularly in the partial withdrawal group. The sample size was small, due in part to the limited numbers of patients who currently take pregabalin for spasticity management and these individual’s hesitation to withdraw from it. Given that all participants were known responders, it is not possible to estimate the applicability of this modality across all individuals with spasticity. Several patients were taking anti-spasticity medications in addition to pregabalin, although the dose of these medications remained constant throughout the study. If anything, the continuation of other anti-spasticity medications may have mitigated the effect of pregabalin withdrawal in this study. Finally, two patients had their daily assessment scores completed by their carers, one of whom did chose not to recommence pregabalin at the conclusion of the study period.

Conclusion

This open-label withdrawal trial assessed known pregabalin responders who had been taking the medication for a median of 18 months. Participant VAS and GAB reports indicated that pregabalin improved spasticity management for the majority of patients and that the anti-spasticity effect of pregabalin was not explained by a reduction in neuropathic pain. The withdrawal protocol was effective in identifying those patients who required smaller doses or no pregabalin for spasticity management. The results suggest that a prospective placebo-controlled cross-over trial is warranted to further investigate the role of pregabalin in spasticity management. However, given the lack of change in MAS in this study, the inclusion of subject self-report measures are likely to be necessary in this setting. The incidence of withdrawal seizures in two of the 11 patients in this trial suggests that future pregabalin withdrawal trials should be undertaken at a slower rate than was utilized under this protocol.

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References