ORIGINAL ARTICLE



Association of baseline severity of lower urinary tract symptoms with the success conservative therapy for urinary incontinence in women

Aneta Obloza^{1,2} · Roderick Teo¹ · Emily Marriott¹ · Gillian Parker¹ · Douglas Tincello^{1,3}

Received: 28 May 2018 / Accepted: 24 September 2018 © The International Urogynecological Association 2018

Abstract

Introduction and hypothesis To identify the association between the symptom severity and outcome of conservative management for OAB, SUI and MUI. Conservative treatments are recommended for overactive bladder (OAB), stress urinary incontinence (SUI) and mixed incontinence (MUI). It is unclear whether disease severity affects treatment outcome.

Methods Patients receiving conservative management were reviewed. Disease-specific questionnaires (OAB-q SF, ICIQ-UI SF) and bladder diaries recorded baseline symptoms. Success was defined by Patient Global Impression of Improvement questionnaire (PGI-I) response of "very much better" or "much better". Non-parametric statistical tests and logistic regression were used. **Results** In 50 OAB patients success was associated with lower symptom severity [30 (0–80) vs. 80 (23–100), p = 0.0001], fewer urgency episodes [4 (0–12) vs. 6 (0–11), p = 0.032] and lower ICIQ-UI SF [5.5 (0–20) vs. 15 (0–21), p = 0.002], but higher QoL [67 (20–101) vs. 24 (6–58), p = 0.0001]. In 50 MUI patients, variables were fewer urgency episodes [3 (0–10) vs. 6 (0–16), p =0.004] and lower ICIQ-UI [11 (1–18) vs. 15 (5–21), p = 0.03]. In 40 SUI patients, variables were fewer incontinence episodes [1 (0–4) vs. 2 (0–5), p = 0.05] and lower ICIQ-UI [11 (6–16) vs. 13.5 (11–19), p = 0.003]. Multiple regression confirmed OAB-q QoL [odds ratio (OR) 1.10 (95% confidence intervals 1.04, 1.1)] for OAB, urgency episodes [OR 0.74 (0.56, 0.98)] and ICIQ-UI [OR 0.83 (0.71, 0.98] for MUI and ICIQ-UI [OR 0.57 (0.40, 0.83)] for SUI.

Conclusions Milder baseline disease severity was associated with successful outcome. There is potential for triage at initial assessment to second-line interventions for women unlikely to achieve success.

Keywords Conservative therapy · OAB · Symptom severity · Urinary incontinence

Introduction

Lower urinary tract symptoms (LUTS) in women are prevalent and a significant health problem worldwide [1, 2]. Women present with involuntary leakage on effort or exertion, or on sneezing or coughing (stress urinary incontinence, SUI) or associated with urgency (urge urinary incontinence, UUI) or a mixture of these symptoms [3, 4].

Aneta Obloza aneta.obloza@nhs.net

² Urogynaecology Department, Leicester General Hospital, Gwendolen Road, Leicester LE4 5PW, UK

³ University of Leicester, Leicester, UK

Among available treatment options, conservative treatment incorporating pelvic floor exercises (PFE) and bladder drill for all women who present initially with urinary incontinence, irrespective of the type of symptoms, is recommended as a first-line treatment (https://www.nice.org.uk/guidance/cg171, https://www.ics.org/Publications/ICI_5/INCONTINENCE. pdf, https://uroweb.org/wp-content/uploads/EAU-Guidelines-Urinary-Incontinence-2015.pdf, [5]).

None of the guideline recommendations (https://www.nice. org.uk/guidance/cg171) include an assessment of symptom severity at baseline, but simply recommend a blanket policy. Severity is important to consider whilst counselling a patient to agree upon the most appropriate treatment to meet patient's expectations. There is limited evidence [6, 7] assessing factors influencing treatment response in patients with OAB and/or urge urinary incontinence. Some authors reported successful treatment in patients with fewer severe symptoms based on use of pads and fewer incontinence episodes [8, 9]. Also,

¹ Urogynaecology Department, University Hospitals of Leicester, NHS Trust, Leicester, UK

better outcomes were reported in younger women [10, 11]. For those with symptoms of SUI, conservative management was more successful in educated menopausal women who had fewer incontinence episodes and no previous continence surgery [12]. It is plausible that women with more severe symptoms may not benefit as much from conservative treatment and could be fast tracked to second-line interventions. This would both ease the pressure for clinical service and may prove to be more cost-effective in the long term. We therefore reviewed the outcomes of women receiving conservative management in our clinics to explore urinary symptom severity as a factor associated with a successful outcome.

Methods and materials

This was a retrospective review of outcomes of conservative therapy for women presenting with symptoms of OAB, both wet and dry, and stress, urge or mixed urinary incontinence in a tertiary urogynaecology centre between 2010 and 2016. Patients were identified from a database recording outcomes of conservative treatment clinics led by the continence nurses. Women were divided into three groups based on their urinary symptoms, in accordance with ICS [3] definitions, as OAB, mixed urinary incontinence (MUI) and stress urinary incontinence (SUI). Patients were excluded if they had bothersome pelvic organ prolapse symptoms, previous continence surgery or concomitant bowel function disorders or were already receiving relevant medication for urinary symptoms.

All patients had been offered standardised conservative management, which included lifestyle and behavioural modification advice [13], bladder training [14] and supervised pelvic floor exercises [15]. Validated disease-specific symptom and QoL questionnaires (ICIQ OAB-SF [16], ICIQ-UI SF [17]) and a 3-day bladder diary were used to record symptom severity at baseline.

Treatment intervention for women with SUI symptoms or stress-predomination MUI included one-to-one sessions teaching PFE and assessing their contraction strength. If these were insufficient to control the symptoms, then intravaginal devices or a ring pessary with a knob was considered. Quality of PFE was assessed by asking about a change in urinary symptoms in subsequent visits and by the Modified Oxford Grading System [18] during vaginal examination when strength and endurance of muscles were assessed with a 10-s interval.

Intervention for OAB symptoms and urge urinary incontinence included teaching PFE, giving lifestyle advice (avoidance of bladder irritants, spacing out volumes of fluids, insurance of daily fluid intake between 1.5 and 2 l and cessation of drinking 2 h before bed time), and behavioural advice (gradual time interval increase between voids, usage of deferring and distraction techniques, stopping convenience voiding and use of urge suppression techniques).

The intervention lasted between 3 and 6 months, depending on the symptom response and the patient's adherence to given advice. The follow-ups were scheduled 3 monthly unless a patient required additional support, which included telephone sessions.

Treatment outcome was defined as success or failure by using the Patient Global Impression of Improvement (PGI-I) questionnaire [19]. Success was defined by the responses "very much better" or "much better" at the end of treatment. Three-day bladder diary data on urinary urgency, incontinence episodes and micturition frequency were calculated for each day per client and then averaged over the 3 days, and the median of the averages was obtained for each group.

SPSS v24 software was used for statistical analysis. Nonparametric tests (Kruskall-Wallis and Mann-Whitney U test) were used to compare data between groups. Logistic regression was performed with success/failure as the dependent variable to identify factors independently associated with treatment outcome, and receiver-operator characteristic curves (ROC) were plotted to estimate sensitivity and specificity for given cut-off values between responders and non-responders.

No ethical approval was required for this work as it was a retrospective review of current practice in the department.

Results

One hundred forty patients were identified: 50 women with OAB, 50 with MUI and 40 with SUI. Demographic data, urinary symptoms and QoL scores are shown in Table 1. Women with OAB were older than those with MUI or SUI. Urinary frequency and urgency episodes were higher in women with OAB/MUI but ICIQ-UI SF scores were higher in women with MUI.

Urinary diary data and symptom scores at baseline are presented for each group, broken down by success/failure in Tables 2, 3 and 4. Thirty women (60%) with OAB responded to treatment compared with 21 (42%) with MUI and 21 (52.5%) with SUI (p > 0.05, chi squared).

In the OAB group, the women who responded had lower OAB-q symptom severity scores, higher OAB-q quality of life scores, fewer urgency episodes and lower scores on the ICIQ-UI SF than those who failed (Table 2). In the MUI group, the women with successful treatment had fewer urgency episodes and lower ICIQ-UI SF scores at baseline than those who failed (Table 3). In the group with SUI alone, women with successful treatment had lower ICIQ-UI SF scores and fewer incontinence episodes at baseline.

Logistic regression results are shown in Table 5. Multivariate analysis revealed only the OAB-q quality of life score to be independently associated with success [OR 1.10,

Table 1 Demographic data of patients

	Group				
	OAB	MUI	SUI	P value*	
Number	50	50	40		
Age (years)	68.5 (34–90)	56.0 (27-86)	54 (32-80)	0.001	
Urinary frequency	8.0 (4-13)	8 (4–13)	7 (4–10)	0.010	
Incontinence episodes	0.5 (0-10)	1 (0–10)	1 (0-4)	0.858	
Urgency episodes	5 (0-12)	4 (0–16)	2 (0-5)	< 0.001	
OAB-q severity	53.0 (0-100)	48.5 (0-100)	_	0.860	
OAB-q QoL	48.5 (6-100)	58.0 (0-94)	_	0.281	
ICIQ-UI SF	11 (0–21)	15 (1–21)	11 (6–19)	0.004	

Data are median (range). Women with SUI were not given OAB-q to complete *Kruskall-Wallis test

95% confidence intervals 1.04, 1.16 for OAB; urgency episodes (0.74, 95% CI 0.56, 0.98) and ICIQ-UI SF (0.83 95% CI 0.71, 0.98) for MUI; and ICIQ-UI SF (0.57 95% CI 0.40, 0.83) for SUI].

For OAB, ROC analysis showed an OAB-q score optimal cut-off of 51, with 95% sensitivity and 76% specificity. For MUI, ROC analysis gave an optimal cut-off of 3.5 episodes per day for urgency (79% sensitivity, 71% specificity) and a score of 12 for ICIQ-UI SF (92% sensitivity, 50% specificity). For SUI patients, the optimal cut-off was 13 on ICIQ-UI SF (92% sensitivity, 50% specificity).

Discussion

We explored the relationship between baseline symptom severity and the success of conservative management for urinary symptoms. The findings showed that there were significant differences at baseline between women who responded to treatment and those who did not. Greater symptom severity for urgency episode frequency, incontinence episode

	Success group	Failed group	P value
Number	30	20	
Age (years)	68 (37–90)	69.5 (34–86)	0.641
Urgency episodes	4 (0–12)	6 (0–11)	0.032
Incontinence episodes	0 (0–10)	1 (0-8)	0.180
Micturition frequency	7 (0–12)	8 (5–13)	0.102
OAB symptom severity	30 (0-80)	80 (23-100)	0.0001
OAB HRQL	67 (20–100)	24 (6-58)	0.0001
ICIQ-UI	5.5 (0-20)	15 (0-21)	0.002

Data are median (range). Women with SUI were not given OAB-q to complete

*Kruskall-Wallis test

frequency and relevant symptom score scales in the relevant patient groups were found to be associated with failure of treatment. In other words, women with OAB and worse OAB symptoms were more likely to fail treatment, and women with SUI and worse incontinence episodes were likely to fail, which is consistent with already published data [12, 20]. We also found a higher OAB quality of life score (indicating better QoL) was strongly associated with success of treatment, although this relationship did not occur in women with MUI.

The definition of LUTS severity is not well established yet. Ghei et al. [21] described the severity of OAB as urgency and urge incontinence depending on circumstances in which these symptoms occurred. The observed pattern of latchkey/walking, running water/cold and mood helped to grade OAB from mild to moderate to severe. In drug studies [22, 23], a higher number of episodes of urgency and incontinence was associated with a greater chance of successful therapy. However, this is not a consistent finding [24].

On the other hand, assessment of SUI symptom severity was examined more extensively. The authors [25–27] used various tools [PGI severity, PRAFAB-Q, SUI subscale of

Table 3 Baseline data compared	d by outcome for MUI wome
---------------------------------------	---------------------------

	Success group	Failed group	P value
Number	21	29	
Age (years)	55 (52-62)	58 (52-63)	0.6
Urgency episodes	3 (0–10)	6 (0–16)	0.004
Incontinence episodes	1 (0-8)	1 (0–10)	0.4
Micturition frequency	7 (4–13)	9 (4–12)	0.7
OAB symptom severity	40 (0-80)	57 (0-100)	0.18
OAB HRQL	55 (32–94)	61 (0–91)	0.3
ICIQ-UI	11 (1–18)	15 (5–21)	0.03

Data are median (range). Women with SUI were not given OAB-q to complete

*Kruskall-Wallis test

men

	Success group	Failed group	P value
Number	21	19	
Age (years)	54 (42–72)	58 (43-80)	0.1
Urgency episodes	1 (0-4)	2 (0-5)	0.1
Incontinence episodes	0 (0–1)	2 (0-4)	0.05
Micturition frequency	6 (0-8)	7 (6–8)	0.1
ICIQ-UI	11 (6–16)	13.5 (11–19)	0.003

Data are median (range). Women with SUI were not given OAB-q to complete

*Kruskall-Wallis test

pelvic floor distress inventory (PFDI)], implying that it may influence the outcome of conservative treatment. When the ICIQ-UI questionnaire [28] was used, the cut-off scores for SUI severity were determined as slight (1–5), moderate (6– 12), severe (13–18) and very severe (19–21).

Other variables that may influence successful outcomes after PFE for SUI such as patient demographic factors, including age, BMI, parity, obstetric history, symptom duration and previous hysterectomy, were reported [10, 11, 25]. However, we only observed that women with OAB were older than those suffering from MUI or SUI but the analysis showed no influence of age upon treatment outcome. Women with poor baseline pelvic floor muscle strength were less likely to report symptom improvement [29] and were more likely to drop out of treatment after 3 months [30]. Other studies [31, 32] reported the greatest improvement in outcome measures among women with the lowest pelvic floor muscle strength at baseline. Fewer data exist for women with OAB having PFE plus bladder training.

All of the above factors are markers of patient status and not indicators of disease severity. We have focussed on severity of symptoms and the associated quality of life disturbance in this preliminary analysis partly because complete data on the above factors were not routinely collected by our nursing staff in their clinical consultations. We acknowledge this as a weakness, and our findings require confirmation from a large prospective cohort study, where all potentially relevant patient demographic data are recorded and included in multivariate analyses and regression to identify independent predictors.

Labrie et al. [25] recently published a study attempting to develop a predictive tool to identify women who proceeded to surgery after conservative treatment for SUI as a surrogate

Table 5 Results of logistic regression analysis

	Univariate analysis	Multivariate analysis	ROC cut-off	Sensitivity	Specificit
OAB					
Age (years)	1.07 (0.96, 0.18)				
Urinary frequency	0.85 (0.53, 1.35)				
Urgency episodes	1.11 (0.80, 1.54)				
Incontinence episodes	0.98 (0.59, 1.65)				
OAB-q severity	0.98 (0.94, 1.02)				
OAB-q QoL	1.09 (1.02, 1.16)	1.10 (1.04, 1.16)	> 51	95%	76%
ICIQ-UI SF	0.89 (0.76, 1.04)				
MUI					
Age (years)	1.03 (0.96, 1.11)				
Urinary frequency	1.38 (0.90, 1.93)				
Urgency episodes	0.56 (0.36, 0.87)	0.74 (0.56, 0.98)			
Incontinence episodes	1.28 (0.85, 1.93)				
OAB-q severity	1.00 (0.96, 1.04)				
OAB-q QoL	0.97 (0.93, 1.03)				
ICIQ-UI SF	0.74 (0.58, 0.93)	0.83 (0.71, 0.98)	≤ 12	57%	86%
SUI					
Age (years)	0.95 (0.87, 1.03)				
Urinary frequency	1.10 (0.62, 1.95)				
Urgency episodes	0.94 (0.49, 1.79)				
Incontinence episodes	0.62 (0.25, 1.52)				
OAB-q severity	_				
OAB-q QoL	_	_			
ICIQ-UI SF	0.56 (0.37, 0.85)	0.57 (0.40, 0.83)	≤13	92%	50%

marker of treatment failure. They found younger age, higher educational attainment and worse symptoms on the Sandvik Index and the Urological Distress Inventory to be associated with progress to surgery, findings that agree with our data for women with SUI. However, there may be other patient factors affecting the decision to accept surgery, so this may not be an entirely useful surrogate indicator of treatment failure per se.

Patient-based definitions of success are bound to be subjective whether they are verbal responses or formal patient reported outcomes (PROs). A wide variety of instruments have been used [6] but they are all satisfaction or improvement based and thus will be influenced by baseline severity. Some data do exist suggesting greater baseline incontinence episode frequency is associated with reported failure in women with detrusor overactivity treated with botulinum toxin [11]. Ideally, any assessment of treatment response needs to be adjusted for baseline severity, something we were unable to do here.

Conclusion

We acknowledge that these are retrospective data without a defined definition of success and that data on all patient demographic data that may be relevant were not included and so the analysis and conclusions must be tentative. The regression analysis was done with a relatively small sample, so the odds ratios for many of the items are small and close to unity, with confidence intervals that demonstrate borderline significance. The data must be regarded with caution, but they do demonstrate the potential to develop a screening tool or algorithm for baseline triage if the findings can be confirmed in a larger prospective study, like that proposed by Labrie et al. [25], but relevant for all symptom groups. Similarly, the ROC analysis demonstrates potential for these items to have discriminatory function and suggest that baseline characteristics may be a useful triage tool to allow individualised treatment plans to achieve greater efficiency by directing patients to treatment modalities that are more likely to be effective. Clearly, further work is required in a prospective study to confirm these findings.

We are aware of one planned study to explore the development of a triage tool to predict treatment success in women with stress incontinence [33]. The results of this study are awaited, but it is clear that a mechanism to predict women who will not benefit from conservative treatment and can be triaged directly to consider medication or surgical intervention has potential for improving the efficiency of clinical service provision as well as showing greater cost-effective use of limited resources.

Compliance with ethical standards

This work took place at the Leicester General Hospital NHS Trust, UK. No ethical approval was required for this work.

Conflicts of interest None.

References

- Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int. 2011;108(7):1132–8.
- Milsom I, Coyne KS, Nicholson S, Kvasz M, Chen CI, Wein AJ. Global prevalence and economic burden of urgency urinary incontinence: a systematic review. Eur Urol. 2014;65(1):79–95.
- Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61:37–49.
- Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29:4–20.
- Practice Bulletin no. 155: Urinary incontinence in women. Obstetrics and Gynecology. 2015;126(5):e66–e81.
- Goldman HB, Wyndaele JJ, Kaplan SA, Wang JT. Defining response and non-response to treatment in patients with overactive bladder: a systematic review. Curr Med Res Opin. 2014;30(3):509– 26.
- Chapple CR, Kelleher CJ, Evans CJ, Kopp Z, Siddiqui E, Johnson N, et al. A narrative review of patient reported outcomes in overactive bladder: what is the way of the future? Eur Urol. 2016;70:799– 805.
- Burgio KL, Goode PS, Locher JL, Richter HE, Roth DL, Wright KC, et al. Predictors of outcome in the behavioural treatment of urinary incontinence in women. Obstet Gynecol. 2003;102:940–7.
- Cammu H, van Nylen M. Pelvic floor exercises: 5 years later. Urology. 1995;45:113–8.
- Burgio KL, Whitehead WE, Engel BT. Urinary incontinence in elderly: bladder sphincter biofeedback and toileting skills training. Ann Intern Med. 1985;104:507–15.
- Owen RK, Abrams KR, Mayne C, Slack M, Tincello DG. Patient factors associated with Onabotulinum toxin A treatment outcome in women with detrusor overactivity. Neurourol Urodyn. 2017;36: 426–31.
- Schaffer J, Nager CW, Xiang F, Borello-France D, Bradley CS, Wu JM, et al. Predictors of success and satisfaction of non-surgical therapy for stress urinary incontinence. Obstet Gynecol. 2013;120(1):91–7.
- Ostaszkiewicz J, Chestney T, Roe B. Habit retraining for the management of urinary incontinence in adults. Cochrane Database Syst Rev. 2004;(2):CD002801.
- Wallace SA, Roe B, Williams K, Palmer M. Bladder training for urinary incontinence in adults. Cochrane Database Syst Rev. 2004;(1):CD001308.
- Dumoulin C, Hay-Smith EJC, Mac Habée-Séguin G. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2014;(5):CD005654.
- Jackson S, Donovan S, Brookes S, Eckford S, Swithinbank L, Abrams P. The Bristol lower urinary tract symptoms

questionnaire: development and psychometric testing. BJU. 1996;77:805-12.

- Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn. 2004;23(4):322–30.
- Laycock J. Clinical evaluation of the pelvic floor. In: Schussler B, Laycock J, Norton P, Stanton SL, editors. Pelvic floor re-education. London: Springer-Verlag; 1994. p. 42–8.
- Srikrishna S, Robinson D, Cardozo L. Validation of the patient global impression of improvement (PGI-I) for urogenital prolapse. Int Urogynecol J. 2010;21(5):523–8.
- Hendriks EJ, Kessels AG, de Vet HC, Bernards AT, de Bie RA. Prognostic indicators of poor short-term outcome of physiotherapy intervention in women with stress urinary incontinence. Neurourol Urodyn. 2010;29:336–43.
- Ghei M, Malone-Lee J. Using the circumstances of symptom experience to assess the severity of urgency in the OAB. J Urol. 2005;171:972–6.
- 22. Chapple C, Khullar V, Nitti VW, Frankel J, Herschorn S, Kaper M, et al. Efficacy of the beta3-adrenoreceptor agonist mirabegron for the treatment of overactive bladder by severity of incontinence at baseline: a post-hoc analysis of pooled data from three randomised phase 3 trials. Eur Urol. 2015;67:11–4.
- 23. Hsiao SM, Lin HH, Kuo HC. Factors associated with a better therapeutic effect of solifenacin in patients with overactive bladder syndrome. Neurourol Urodyn. 2014;33(3):331–4.
- 24. Serati M, Braga A, Siesto G, et al. Risk factors for the failure of antimuscarinic treatment with solifenacin in women with overactive bladder. Urology. 2013;82:1044–8.

- 25. Labrie J, Lagro-Jassen ALM, Fischer K, et al. Predicting who will undergo surgery after physiotherapy for female stress urinary incontinence. Int Urogynecol J. 2015;26:329–34.
- Hendricks EJM, Kessels AGH, de Vet HCW, et al. Prognostic indicators of poor short-term outcome of physiotherapy intervention in women with stress urinary incontinence. Neurourol Urodyn. 2008;27(5):379–87.
- 27. Schaffer J, Nager CW, Xiang F, et al. Predictors of success and satisfaction of non-surgical therapy for stress urinary incontinence. Obstet Gynecol. 2012;120(1):91–7.
- Klovning A, Avery K, Sandvik H, Hunskaar S. Comparison of two questionnaires for assessing the severity of urinary incontinence: the ICIQ-UI SF versus the incontinence severity index. Neurourol Urodyn. 2009;28(5):411–5.
- Bo K, Larsen S. Pelvic floor muscle exercise for the treatment of female stress urinary incontinence: classification and characterisation of responders. Neurourol Urodyn. 1992;11:497–507.
- Neumann PB, Grimmer KA, Deenadayalan Y. Pelvic floor muscle training and adjunctive therapies for the treatment of stress urinary incontinence in women: a systematic review. BMC Womens Health. 2006;6:11.
- Knight S, Laycock J, Naylor D. Evaluation of neuromuscular electrical stimulation in the treatment of genuine stress incontinence. Physiotherapy. 1998;84(2):61–71.
- 32. Turkan A, Inci Y, Fazli D. The short-term effects of physical therapy in different intensities of urodynamic stress incontinence. Gynecol Obstet Investig. 2005;59:43–8.
- 33. Dumoulin C, Desmeule F, Hagen S, Masse BR, Mayrand M-H, Morin M, et al. Development and validation of a clinical prediction rule to guide and improve the treatment of female stress urinary incontinence. http://webapps.cihr-irsc.gc.ca/decisions/p/project_ details.html?appIId=344799&lang=en. Accessed 13 Apr 2018.