Topiramate attenuates self-injurious behaviour in Prader–Willi syndrome

Nathan A. Shapira¹, Mary C. Lessig¹, Tanya K. Murphy¹, Daniel J. Driscoll² and Wayne K. Goodman¹

¹ Department of Psychiatry, Evelyn F. and William L. McKnight Brain Institute of the University of Florida, Gainesville, FL, USA
² Department of Pediatrics and Center for Mammalian Genetics, University of Florida, Gainesville, FL, USA

Abstract

Self-injurious behaviour (SIB), most notably skin picking, has been described by various terms in the literature ranging from neurotic/psychogenic excoriations to compulsive/pathological skin picking. Prader–Willi Syndrome (PWS) is a neurogenetic multisystem disorder characterized by infantile hypotonia, mental retardation, short stature, hypogonadism, dysmorphic features, and hyperphagia with a high risk of obesity. Psychiatric manifestations include SIBs in the form of skin picking, nail biting and rectal gouging. Topiramate is a novel anti-epileptic medication without significant liability of weight gain. There are no published reports of topiramate being utilized in PWS or SIB. We report attenuation of SIB with resultant lesion healing in three PWS adults treated with topiramate in an 8-wk open-label trial. Although our findings should be treated with caution, they suggest that double-blind or cross-over studies with topiramate are warranted to establish the possible role of topiramate in attenuating SIB in PWS and other disorders that involve SIB.

Key words: Anti-epileptic, Prader–Willi syndrome, self-injury, skin picking, topiramate.

Introduction

Self-injurious behaviour (SIB), most notably skin picking, has been described by various terms in the literature ranging from neurotic/psychogenic excoriations (NE) to compulsive/pathological skin picking (Arnold et al., 2001; Stein and Simeon, 1999). Often reported in the dermatological literature, SIB has also been characterized as an obsessive–compulsive-related or impulse control-related disorder (Arnold et al., 2001; Stein et al., 1993). SIB in the form of skin picking usually presents as an uncontrollable desire to rub or pick at one's skin resulting in ulcerated lesions that often become infected and lead to more serious medical conditions such as sepsis (Koo, 1992). These urges are often precipitated by an ‘itchiness’, an irregularity of the skin (e.g. an insect bite or acne), or as in one case report, due to the patients desire to ‘hear’ her hand rubbing skin (Parsad and Saini, 1997). Proposed treatments have included antipsychotic medications, benzodiazepines, clomipramine, conventional antihistamines, doxepin, inositol, naltrexone, selective serotonin reuptake inhibitors (SSRIs), topical glucocorticoid antibiotics, and psychotherapy (Arnold et al., 2001; Gupta and Gupta, 1993; Koo, 1992; Seedat et al., 2001).

Prader–Willi Syndrome (PWS) is characterized by infantile hypotonia, mental retardation, short stature, hypogonadism, dysmorphic features, and hyperphagia with a high risk of obesity (Holm et al., 1993). Also frequently observed in PWS are behavioural and psychiatric manifestations including self-injury (e.g. gouging, nail biting, and skin picking), explosive outbursts, oppositional behaviour, obsessive ruminations, and compulsive behaviours including hoarding, counting, and arranging (Cassidy et al., 1997; Dykens et al., 1999). PWS usually results from a deletion on the paternal chromosome 15q11–q13 or maternal uniparental disomy of chromosome 15 (Glenn et al., 1997). It was first described in 1956 (Prader et al., 1956) and the physical (e.g. the obesity-related cardiovascular diseases) and behavioural problems (e.g. SIB) result in the major causes of morbidity and mortality (Martin et al., 1998).

Small open-label studies have demonstrated that SSRIs can be helpful for a wide range physical, behavioural and psychiatric problems including self-injurious, aggressive, affective, and compulsive behaviours associated with PWS (Benjamin and Buot-Smith, 1993; Hellings and Warnock, 1994; Warnock and Kestenbaum, 1992). Unfor-
Unfortunately, SSRIs can exacerbate aggressive, repetitive, and compulsive behaviours in PWS during initiation or titration phases (Martin et al., 1998). Data from a systematic survey of the 369 caretakers of PWS participants showed that of the 18.7% receiving medication, SSRIs appeared the most helpful in treating compulsions and temper outbursts while antipsychotics were most helpful in skin picking and compulsions (Stein et al., 1994). Antiepileptic and antipsychotic medications are sometimes helpful in PWS patients (Durst et al., 2000; Verhoeven et al., 1998) targeting impulsive and psychiatric behaviour, although as a whole they have a tendency to increase weight.

Topiramate \( [2,3:4,5\text{-bis-O-(1-methylethylidene)-}\beta\text{-d-fructopyranose sulphamate} ] \) is a novel agent approved for the treatment of epilepsy, which does not have the typical weight-gain liability of antiepileptics (Privitera, 1997). Common side-effects of topiramate include fatigue, difficulty concentrating, parathesia, somnolence, ataxia, dizziness, weight loss, and an increased incidence of nephrolithiasis consistent with the fact that topiramate is a carbonic anhydrase inhibitor (Privitera, 1997). Several possible mechanisms of action have been identified for topiramate (Privitera, 1997): (1) state-dependent blockade of voltage-activated \( \text{Na}^+ \) channels; (2) facilitation of \( \gamma\text{-aminobutyric acid (GABA}_{\text{A}} \) receptors; and (3) antagonism of kainate/AMP-A-type glutamate receptors. Currently, there are no published reports of topiramate being utilized in PWS or SIB. We report the attenuation of SIB in three PWS adults treated with topiramate in an 8-wk open-label trial resulting in lesion healing.

Methods and results

This project was reviewed and approved by the Institutional Review Board of the University of Florida Health Science Center and all participants provided written informed consent. The participants were between 18 and 65 yr. PWS is often characterized by mild mental retardation. In this study only those individuals who were capable of providing their own informed consent were included. Criteria for exclusion included: clinically significant suicidality or homicidality; current or recent (within 6 months of starting of topiramate) DSM-IV diagnosis of substance abuse or dependence; a clinically unstable disease that could interfere with treatment or assessment of PWS; treatment with any drug that might interact adversely with topiramate; and personal or family history of nephrolithiasis. Women of childbearing potential who were not taking adequate contraceptive measures were not included. Screening measures included a physical examination, psychiatric background, medication history, blood drawn for laboratory assessment (CBC, SMA-12, urinalysis, and a B-hCG for women of childbearing potential), and the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-P). Weekly assessments of weight loss, participant functioning, and safety measures, including blood pressure and pulse, were taken by the investigators at each visit. Participants are residents of group homes operated by the Association of Retarded Citizens, Alachua County (ARC). These homes are monitored thus allowing recording of participants’ behavioural and psychiatric manifestations as well as their medication management. Due to the nature of PWS and the side-effects profile associated with topiramate, a slow titration rate was utilized to minimize potential side-effects. Participants begin pharmacotherapy with 25 mg of topiramate given in the evening for the first 7 d and then up to 50 mg in evening for the next 7 d. After 14 d, the daily dose could be increased in increments of up to 50 mg/wk although generally the increase was by 25 mg/wk.

Case 1

Ms. A is a 19-yr-old female who through DNA methylation testing was positive for PWS and shown to carry a deletion through FISH and DNA polymorphism analyses. Ms. A has a history of hoarding and severe skin picking dating from childhood. Current concomitant psychiatric medications include 60 mg/d fluoxetine and 50 mg/d naltrexone. Psychiatric intervention dates back to 1992 when the participant began therapy with clomipramine and fenfluramine, both of which were unsuccessful in managing her behaviour and weight problem. Initial side-effects (of topiramate) experienced included mild sedation, word-finding difficulties, and unrelated lower-back pain that resolved by week 8. Ms. A’s weight remained stable with a baseline of 129.5 lb and a weight of 128.5 lb at week 8. Ms. A had a long-standing primary lesion on her right forearm that measured approximately 4 cm × 1 cm and was ulcerated at baseline. She experienced a reduction in skin picking with improvement to the lesions on her face, arm, and legs noted by week 4 (75 mg/d). To better follow the improvement in her skin condition, a photographic record of the lesion on Ms. A’s forearm was begun (Figure 1) demonstrating the healing of the ulceration of this lesion by week 8 of topiramate treatment (150 mg/d).

Case 2

Mr B is a 29-yr-old male confirmed as carrying a chromosomal deletion as described above. He has a history of severe food seeking and skin picking dating...
Topiramate attenuates SIB in PWS

Ms. A on 75 mg/d topiramate (right arm), week 4

Ms. A on 150 mg/d topiramate (right arm), week 8

Mr. B on 25 mg/d topiramate (left arm), week 1

Mr. B on 200 mg/d topiramate (left arm), week 8

Ms. C (right breast), baseline

Ms. C on 175 mg/d (right breast), week 8

Figure 1. Illustrations of subjects’ primary SIB lesions.

from childhood. Mr. B does not have a history of taking psychotropic medications. He had declined a previous recommendation to take fluoxetine. Initial healing of his primary lesion (a round 1.5 cm diameter ulcerated lesion) was noted within 1 wk of initiating topiramate treatment (25 mg/d) at which point photographic records were started (Figure 1). Mr. B experienced some increased irritability at topiramate initiation, with this irritability returning towards baseline by week 8. Mr. B experienced a decrease in his weight from 180.0 lb at baseline to 176.8 lb at week 8. By week 8 of topiramate treatment (200 mg/d), Mr. B had experienced remission of his SIB with resultant healing and complete recovery of the ulceration of his primary lesion (Figure 1).
Ms. C is a 32-yr-old female confirmed as carrying a chromosomal deletion as described above. Concomitant psychotropic medications include 20 mg/d fluoxetine. She has a history of food seeking and skin picking dating from childhood. Due to her employment, Ms. C picks in multiple concealed locations (e.g., her chest, breasts, and the top of her legs). Because of her secrecy regarding SIB, the staff members of her group home perform full body surveys daily. As a result of previous experience with Ms. A and Mr B, photographic records of her lesions were started prior to initiation of topiramate. After beginning topiramate treatment, an attenuation of SIB and number of ulcerated lesions (Figure 2) was noted within 1 wk (25 mg/d) by photographs and by 2 wk (50 mg/d) by her group home staff. Side-effects included word-finding difficulty, mild confusion, sedation, and some mild tingling in her left heel. All side-effects resolved by week 5. On topiramate treatment Ms. C experienced an increased weight from 150 lb at baseline to 154 lb at week 8. At week 8, Ms. C had continued attenuation of skin picking on a dose of 175 mg/d (Figures 1 and 2). During participation, Ms. C experienced a period of 3 wk where she was without any SIB. However, reportedly as result of her picking at several insect bites, small ulcerated lesions appeared on her forearm and lower legs in weeks 7 and 8 (Figure 2).

### Discussion

We report on three cases in which the antiepileptic topiramate appeared beneficial in attenuating SIB in a patient population where SIB is common and difficult to manage and treat. There are several limitations to this report. These include, first, topiramate treatment being an open-label study of small sample size. Second, it was added in two participants to concomitant psychotropic medications. Third, the selective photography of lesions was only started prior to topiramate initiation in one participant (Ms. C). Fourth, typical dosages for topiramate used for seizure treatment are higher than those reported in these participants and the mild resurgence in Ms. C’s lesions may be a result of too low a dose. Finally, it cannot be ruled out that topiramate’s action in these participants was through a mechanism improving skin healing and not through decreased SIB because the investigators did not directly observe participants’ SIB.

There are several factors that help to mitigate these limitations. While this is an open-label study, all three participants in this report have PWS through a deletion in chromosome 15q11–q13, have long-standing self-injury, and two participants (Ms. A and Ms. C) had failed previous psychotropic medication interventions. Furthermore, all three PWS participants chose to continue topiramate treatment after the 8-wk trial (10 months for Ms. A, 9 months for Mr B, and 6 months for Ms. C) with continued improvement in self-injury. Improvement in self-injury was not only noted by investigators, but by systematic body evaluations by the group home in one participant (Ms. C). Additionally, while individuals with PWS often pick surreptitiously and even when they describe having no urges, all three participants reported to the investigators a decreased urge to pick while on topiramate treatment. Finally, in terms of an objective measurement of impulsivity, participants were also followed by the Delay Task of the computerized Gordon Diagnostic System (Gordon et al., 1996). The Delay Task measures a participant’s ability to suppress and delay impulsive behavioural responses (Gordon et al., 1996). All three participants demonstrated improvement in the Delay Task while on topiramate treatment.

The mechanism by which topiramate might attenuate SIB in PWS is unknown. There are a few reports of antiepileptic medications being specifically used for SIB. These include carbamazepine demonstrating decreased self-mutilation in Lesch–Nyhan Syndrome patients (Roach et al., 1996) and lamotrigine demonstrating improvement in SIB in an adolescent with profound mental retardation (Davanzo and King, 1996). SIB occurs in a majority of PWS individuals, particularly those who are older and where the PWS resulted from a chromosomal deletion (Cassidy et al., 1997; Dykens et al., 1999). While a direct relationship between SIB in PWS and topiramate’s mechanism(s) of action is unknown, it is interesting that in the PWS chromosomal deletion region there are loci which code for GABA<sub>xA</sub> receptor subunits (Greger et al., 1995) and that one of topiramate’s proposed mechanisms of action is to increase the activity of GABA<sub>xA</sub> receptors by enhancing GABAergic function at the non-benzodiazepine site (Privitera, 1997).
Although our findings should be treated with caution, they suggest that double-blind or cross-over studies with topiramate are warranted to establish the possible role of topiramate in attenuating SIB in PWS and other disorders that involve SIB.

Acknowledgements

This work was supported by the Prader–Willi Syndrome Association (USA) and the University of Florida College INCENTIVE Fund.

References


