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Review

Topiramate-associated sexual dysfunction: A systematic review☆

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ABSTRACT

Introduction: Sexual pharmacotoxicity renders patients with epilepsy at a risk for sexual dysfunction (SD). This study is aimed to analyze the relationship between sexual function and topiramate to avoid topiramate-associated SD.
Methods: A systematic review following the PRISMA guidelines was performed to elucidate any SD occurrence in patients receiving topiramate.
Results: A total of 17 publications were reviewed. Based on limited polytherapy observational studies, the frequency of self-reported topiramate-associated SD, libido disorder, and orgasmic disorder in patients with polytherapy was 9.0%, 9.0%, and 2.6%, respectively (grade C evidence). Female patients mainly had anorgasmia, whereas male patients principally had erectile dysfunction. The daily dose of topiramate in patients with SD was within the recommended dose. Sexual adversity usually occurred from 4 weeks after topiramate use but favorably subsided without eventful complications after topiramate substitution or dose reduction in all patients.
Conclusions: Topiramate can elicit different patterns of SD, especially anorgasmia in women and erectile dysfunction in men, even with a therapeutic dose. Detailed drug education and careful monitoring are necessary to maximize sexual health, especially in persons undergoing polytherapy and with other risks for SD. Moreover, a rapid response, such as substitution or reduction of the dose, is suggested when SD occurs during its use.

1. Introduction

Persons with epilepsy are known to have a higher frequency of sexual dysfunction (SD) than their healthy peers [1]. Therefore, sexual pharmacotoxicity should be seriously treated to protect and maximize sexual health, especially in young and vulnerable persons. Topiramate (CAS 97240-79-4; $C_{12}H_{21}NO_8S$) is popularly prescribed for generalized tonic–clonic seizure [2], as well as for refractory [3] and nonrefractory focal seizure [4], as monotherapy or adjunctive therapy. It is also the first-line treatment for migraine, and commonly used as single or combined therapy for bipolar disorder, alcohol-use disorder, and a variety of neuropsychiatric disorders [5] that usually occur in sexually active persons. The annual prescription of topiramate greatly exceeds that of other newer-generation antiepileptic drugs such as pregabalin, lamotrigine, levetiracetam, and valproate sodium [6], possibly owing to the broad indication of topiramate in practice.

Topiramate is inactive for a wide group of receptors or neurotransmitter transport systems such as alpha1, alpha2, and beta adrenoceptors; dopamine (DA) 1 and 2 receptors; histamine 1 and 2 receptors; serotonin (5-HT) 1B and 2 receptors; and transporters of DA, norepinephrine (NE), and 5-HT [7,8]. However, it still has multiple mechanisms of action specific to its epileptic effect [9,10]. It can potentiate the gamma-aminobutyric acid (GABA) activity of neurons through opening of the chloride ion channel on the nonbenzodiazepine site of the $GABA_A$ receptor [11]. Recently, topiramate use was found to elevate the brain GABA level in humans [12]; however, such relationship is controversial in ex vivo studies [13]. Topiramate does not bind with the *N*-methyl-D-aspartate (NMDA) receptor but blocks the kinate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors through an inhibition of protein kinases and dephosphorylation to reduce glutamate release [14]. The binding site is mainly the GluR5 subunit in the kinate receptor [15] and the GluR1 subunit in

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the AMPA receptor [16]. In addition, topiramate potently inhibits the voltage-activated sodium, potassium, or L-type calcium channels [8–10], and weakly inhibits the carbonic anhydrase isoenzymes [12,17]. These pharmacological properties construct a hyper-GABAergic and hypoglutamatergic status in patients taking topiramate.

In ex vivo studies, chronic exposure to 100 mg/kg topiramate for 60 days caused a reduction of spermatogenesis, sperm motility and density, weight of reproductive organs, blood testosterone level, mating frequency, and female impregnation in adult male rats [18], suggesting that topiramate negatively affects sexual function. Recently, sexual desire [19], arousal [20,21], orgasm [22,23], and romantic love [24,25] in humans were subsequently found to be variably involved with the mesocorticolimbic circuit and corticostriatal loop. This is counterbalanced by excitatory neurotransmitters and neuropeptides such as DA, NE, and glutamate, as well as inhibitory neurotransmitters and neuropeptides such as GABA and 5-HT. Therefore, topiramate may jeopardize sexual function and related behavior through its hyper-GABAergic–hypoglutamatergic effect. Unfortunately, modern knowledge of topiramate-associated SD comes from only a few clinical cases [26]. This paucity in data may cause professionals to misunderstand topiramate as having high sexual safety like other commonly used drugs [27]. Therefore, we reviewed the current literature to elucidate the relationship between sexual function and topiramate, in order to better predict and avoid SD in topiramate-treated patients.

2. Methods

The aim of this study was to elucidate the relationship between topiramate and sexual function in humans. To cover all aspects of topiramate-associated SD, any sexual adversity related to topiramate reported in the literature was included and categorized in this study.

2.1. Types of SD

SD included any of the sexual disorders listed in the Diagnostic and Statistical Manual of Mental Disorders (fifth edition), or disorders related either to changes in the sexual response cycle, or impairments of the genitalia or reproductive organs that interfere with sexual activity. Isolated cases of sexual dissatisfaction without psychobiological disturbance were not included.

2.2. Drugs and effects

Topiramate might increase, decrease, deviate, or improve sexual function. In this study, any negative impact of sexual function was reviewed. The following studies were considered concerning the relationship between topiramate and sexual function:

1. Clinical trials reporting changes in sexual function;
2. Comparative studies evaluating sexual function between patients taking topiramate and healthy controls or patients who are not taking these agents; and
3. Case reports describing changes in sexual function after topiramate use.

2.3. Topiramate

Since the expiration of the patent of topiramate, many generic drugs have been marketed under different commercial names worldwide. To minimize incomplete coverage, we searched the brand name, chemical name, and commercial name of topiramate as listed in the United States Food and Drug Administration, Taiwan Food and Drug Administration, Medicines and Healthcare Products Regulatory Agency of the United Kingdom, European Medicines Agency, and Medindia (http://www.medindia.net/index.asp).

2.4. Literature search

A systematic literature search related to sexual function and topiramate was performed following the guideline of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses). All papers, books, proceedings, and abstracts that were published until October 2016 were considered in this study but were required to be full-text manuscripts, book chapters, and abstracts containing the type of SD, and to have English or Chinese titles.

A computer-based search of the literature was performed by using a cross-match of topiramate and a list of keywords in scientific databases. The keywords used were “sexual desire”, “libido”, “sexual arousal”, “orgasm”, “anorgasmia”, “ejaculation”, “impotence”, “erectile dysfunction”, “vaginismus”, “hyposexuality”, “hypersexuality”, “paraphilia”, “sexual misconduct”, “priapism”, “sexual dysfunction”, “sexual deviation”, “sexual behavior”, “sexual intention”, “sexual motivation”, “sexual dissatisfaction”, or “sexual function”. The following scientific databases were searched: ProQuest, PubMed, Scopus, Embase, Cochrane Database of Systematic Reviews, and the Chinese databases including the Taiwan Periodical Literature System (http://readopac.ncl.edu.tw/nclJournal) and the Airiti Library (http://www.airitilibrary.com).

Additionally, the references of all manuscripts, book chapters, and proceedings were further reviewed to ensure maximal coverage of the literature. Moreover, alerts and new announcements from the official websites of the United States Food and Drug Administration, Taiwan Food and Drug Administration, Medicines and Healthcare Products Regulatory Agency of United Kingdom, and European Medicines Agency were also carefully reviewed for any concern.

2.5. Level of evidence

The level of evidence (LOE) and grade of evidence (GOE) were adopted from the Oxford Centre for Evidence-based Medicine.

2.6. Statistical analysis

Categorical variables were analyzed by using unpaired Student's t-test. A probability of <0.05 was considered significant.

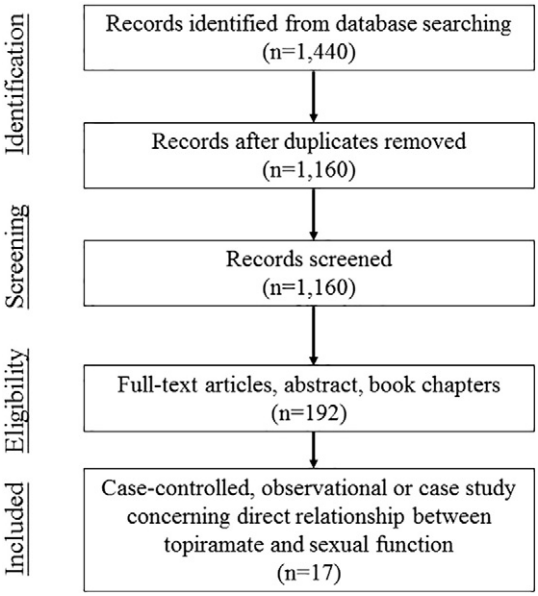

Fig. 1. The flow-chart of literature search.