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Editorial

Look at the drug-induced sexual dysfunction in male patients with stroke: a critical appraisal

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Given that risk factors for stroke, including hypertension, cardiomyopathy, dyslipidemia and diabetes, should be well managed to prevent primary events or recurrences, patients with stroke are often treated with several drugs [1]. To deal with cognitive and behavioral dysfunction following stroke, such as depression, agitation and anxiety, patients may be prescribed psychotropic drugs [2].

Moreover, prevalence of post-stroke seizures is high, especially due to cortical lesions, and antiepileptics are often used to prevent and or manage symptomatic stroke-related epilepsia [3].

If on one hand pharmacotherapy is fundamental to better manage the disease and its potential complications, on the other hand most drugs may cause sexual dysfunction (SD).

Antihypertensive compounds are known to frequently cause SD, including erectile dysfunction (ED), ejaculation disorders and reduced sexual desire. Angiotensin II receptor antagonists, when combined to diuretics, exert the most devastating effect on sexual function [4]. Diuretics seem to impair sexuality through different and still not-well known mechanisms, including lowering of blood volume and flow, and decreasing electrolytes. Thiazides, in particular, are believed to also decrease sexual hormone levels, and thus sexual desire, by acting on serum zinc levels. Also betablockers, but nebivolol, often determine ED, due to their action on the adrenergic system whose balance with the cholinergic pathway is fundamental for vasogenic erection to exist [5]. Calcioantagonists and ACE-Inhibitors have the best profile, leading to fewer sexual side effects than the other drugs [4]. Although the relationship between vascular risk factors, antihypertensive drugs and SD is complex and multifactorial, this issue is still under-investigated in clinical practice, especially when dealing with patients with stroke, who often have several cardiovascular risk factors and are under polytherapy [6]. Thus, these potential sexual side effects of antihypertensives should be taken into consideration when treating patients with stroke, especially when males and young. When it is not possible to prescribe less harmful antihypertensives, the use of phosphodiesterase 5 inhibitors (PDE-5i) is of help in the case these are not contraindicated.

Several psychotropic drugs may be used in patients following stroke to manage depression, anxiety, aggression, agitation, and other behavioral problems. These compounds are known to cause SD, and the odd-ratio is higher in this patient population because the neuro-vasogenic mechanism of erection is often impaired by the common vascular risk factors [6]. A recent systematic review by Trincheri *et al.* [7] found a significant association between SD and antidepressants, being SNRI more likely to cause ED. Few data were available regarding the effects of antipsychotics male sexual function, with risperidone showing higher odds ejaculatory dysfunction [7].

Among antidepressants, selective serotonin reuptake inhibitors (SSRI) are those causing SD more frequently, especially ejaculatory disorders and anorgasmia. This is probably due to a more evident imbalance of the dopamine/serotonin ratio, as dopamine exerts a positive effect on sexuality whereas most of the serotonin receptors negatively affect sexual function [8]. Antidepressants with a noradrenergic/dopaminergic profile, as well as the new Serotonin norepinephrine reuptake inhibitors (SNRI) vortioxetine, are indeed known to cause less or no SD, and they should be preferred to treat depression in male patients with stroke.

In fact, when antidepressant-induced SD is diagnosed, the drug dosage should be lowered, and/or switched to other classes, but this often leads to an exacerbation of the depressive symptomatology. There is a bidirectional relationship between sexual function and depression: patients with depression had a higher risk of having SD than the general population, whilst individuals suffering from SD had an increased risk of developing depression [9]. Indeed, the two syndromes have dysfunctions of common neurotransmitter systems, and the drug used to treat depression may worsen and/or improve SD (e.g., SSRI are effective in treating premature ejaculation because they cause delayed ejaculation). One emerging problem with antidepressants is the persistence of SD after the drug had been withdrawn. The so-called post-SSRI syndrome is considered a new challenge because, to date, no specific treatment exists and diagnostic criteria are far from being accepted by the academic world [10].

Antipsychotic drugs can affect male sexuality in different ways. First-generation antipsychotics, as well as risperidone, increase prolactin levels with reduced desire, ED and sometimes gynecomastia. Atypical neuroleptics, such as olanzapine, seems to cause SD by acting on adrenergic and serotonergic systems. Aripripazole is less commonly associated with male SD. Thus, before prescribing these drugs to face behavioral symptoms in post-stroke patients, clinicians should evaluate their pharmacodynamic properties to avoid/reduce the high SD risk.

Old antiepileptics, including carbamazepine and valproate, cause SD (especially loss of libido) through complex mechanisms mainly involving the endocrine system, i.e. by inhibiting the sexual hormone binding globulin and activating the aromatase with a consequent decrease in testosterone and increase in estrogen levels [11]. New antiepileptics (topiramate, pregabalin, oxcarbazepine, levetiracetam, etcc) are known not to cause SD, and they should be preferred when dealing with post-stroke epilepsy in young males. Nonetheless, there are some reports on their potential in inducing different kinds of SD through intricate mechanisms involving the brain neurotransmitters [12].

As sexual function is becoming an indicator of patient's quality of life, all individuals with neurological disorders, including stroke, should be questioned and assessed about SD [13]. Unfortunately, no guidelines on how approaching SD in patients with stroke exists, as there is still poor research on sexual rehabilitation and pelvic floor physiotherapy [14], as well as on the treatment of iatrogenic SD. Future studies should be fostered to pave the way for the management of SD in this patient population.

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