

The Impact of Sodium Valproate on Male Reproductive Health: A Comprehensive Review

Harpreet Singh¹, Gaurav Verma¹, Mohd. Shafi Sheikh¹

¹ CT University, Ludhiana

Corresponding Author's email address: harpreet24118@ctuniversity.in

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Abstract:

Sodium Valproate is one of the most prescribed antiepileptic drugs and it leads to severe reproductive problems among men. The objective of this review is to provide an overview about the influence of valproate on male fertility, testicular morphology and hormonal regulation based on published data. Several studies have reported that chronic treatment with Valproic Acid can cause testicular morphological alterations, decreased sperm mobility and hormonal imbalances, suggesting male infertility. Research with animal models, mostly Wistar rats and Swiss mice, has demonstrated that valproate provokes germ cell damage through oxidative stress- genotoxicity acted induced meiosis. These findings have important implications for understanding the risks of valproate therapy in epileptic men. It also reviews other potential preventive methods, such as antioxidant intervention that would decrease the harmful effects of valproate on reproductive health. Collectively, the evidence presented indicates that healthcare providers should consider these risks when prescribing valproate and investigate alternative treatment options or protective measures for male patients. The purpose of this comprehensive review is to provide information regarding the clinical management and also indicates future research prospects that may be targeted in investigating how valproate use might have reproductive consequences among male population.

Keywords: Valproate, Male Fertility, Reproductive Health

1. Introduction

Valproate (sodium valproate) is also a medication used in the treatment of epilepsy, bipolar disorder and migraine headaches(Iamsaard et al. 2017). It was established in the 1960s and has since been widely used for the treatment of seizures, especially when patients are resistant to other anti-epileptic drugs(Perucca 2012). Although valproate exhibits therapeutic properties, there are concerns about its detrimental impacts on male reproductive health. More research is being dedicated to identify what effects valproic acid has on male fertility and hormonal profile over long term administration(Romoli et al. 2019).

The male reproductive system is highly sensitive to different environmental and pharmacological agents, and the effect of drugs like valproate can be profound(Mascarenhas, Sousa, and Rato 2024). Research demonstrates that males who receive valproate as a treatment often suffer from reproductive problems, such as changes in epididymal structure and these factors may be employed for the prediction of decreased sperm count. For instance, studied male Wistar rats and reported

marked histopathological changes in the testes after long-term treatment with valproate, indicative of morphological structural alterations within the organ (RØste et al. 2001). The changes in fertility were associated with a decreased sperm count and motility, implicating valproate exposure as being directly responsible for impaired fertility (Tallon, O'Donovan, and Delanty 2021).

Valproate impairs male reproductive health both directly and indirectly through multiple mechanisms. One of the suggested mechanisms is oxidative stress, that when there are more reactive oxygen species (ROS) than antioxidant defenses (Walke et al. 2023). High levels of oxidative stress creates cellular damage, through DNA fragmentation and apoptosis of germ cells. In male mice, sodium valproate induced oxidative damage again supports the hypothesis that the reproductive toxicity of this drug may occur via induction of an oxidizing state (Khan et al. 2011). Valproate treatment can also worsen these effects, possibly through a synergistic effect of valproate on any hormonal imbalances (Svalheim et al. 2015). Men with epilepsy receiving valproate show changes in reproductive hormones, including reductions in testosterone levels, an essential factor for both male fertility and overall reproduction functions (RØste et al. 2005).

These findings are potentially relevant, given the growing utilization of valproate in clinical practice. This study highlights reproductive risks of valproate therapy that healthcare providers should be cognizant and vigilant about, especially in men in their childbearing years. This knowledge is critical for planning proper management and counseling of patients on the potential reproductive health consequences of treatment. Indeed, studies have also started to investigate possible protective strategies able to counteract the adverse impact of valproate on male fertility. For example, treatment with antioxidant supplementation has recently been theorized to alleviate oxidative stress and enhance reproductive outcomes in animal models.

The aim of this review was to assemble a series of studies focusing on reproductive outcomes in men with the overarching goal that they provide an overall perspective. This paper aims to review literature available on the use of valproate in men with epilepsy and through synthesizing research conducted, intends to emphasize both the need for male reproductive health considerations while recommending valproate as well as suggest areas for further studies.

2. Main Body

2.1 Morphological and Functional Alterations in the Testis

Diverse researches have been published using animal models to explore the morphological changes caused by valproate (Fereshetyan et al. 2021). Studies reported that Long-term treatment of Wistar rats with sodium valproate leads to cause marked testicular damage. Degeneration in the seminiferous tubules and decrease number of sperm was observed histologically (RØste et al. 2001). These morphological changes are in agreement that demonstrated biochemical changes in reproductive function parameters of male Wistar rats subjected to sodium valproate (Vijay, Yeshwanth, and Bairy 2008).

Furthermore, the semen parameters as well showed harmful effects of valproate on sperm motility and morphology. Numerous studies showed similar findings, though the affected fertile parameters were only sperm motility and testicular volume; with men treated for epilepsy using valproate

demonstrating lower levels of these two characteristics(Hamed et al. 2015). Further investigations described changes in sperm head morphology also appear to be directly related and focused on the permanent injury of germ cells likely induced by valproate(Trivedi et al. 2010).

2.2 Hormonal Imbalance and Oxidative Stress

The effects of sodium valproate on male reproductive health are not only due to the structural changes, but also brought about by hormonal disturbance(Harden and Pennell 2013). Various examinations authenticated that testosterone levels were measured in men treated with valproate and hormone concentrations that had no impact on male reproductive potential(Chen et al. 1992). This hormonal imbalance could lead to the reproductive disturbance. These antiepileptic drugs can affect male reproductive health markedly(Isojärvi et al. 2004).

Valproate's adverse effects are mediated through oxidative stress. A research demonstrated the oxidative harm to germ cells triggered by sodium valproate, indicating that this resulting stress is an important factor in genotoxicity and reduced reproductive ability(Safdar and Ismail 2023). There is growing evidences that vitamin E supplementation might be beneficial as an initial protective strategy in the prevention of valproate-induced testicular injury, and shown a significant decrease in TAC levels; however author detected adequate plasma glutathione (GSH) values which were probably stoichiometrically oxidized at about 90% due to VPA treatment since urine malondialdehyde (MDA) values increased nearly fourfold compared with control group fortifying poor efficiency against peroxidative stress though good capacity present for defense biochemical pathways yet not activated fully as it seem from enzyme antioxidant activity results(Alsemeh et al. 2022).

3. Summary

In conclusion, the information provided from this review clearly demonstrates the significant harmful effects of valproic acid at the male reproductive health. This emphasizes the complexity between pharmacological-reproductive parameter interplay, reviewing morphological testis changes; hormonal imbalance and oxidative stress, which provide further insights. Epidemiological studies have indicated that the use of valproic acid is high for clinical epilepsy, and hence Health Care Practitioners should be made aware about these potential risks while they consult their male patients providing them with other options or minimal strategies to protect from this harm. Additional studies are needed to elucidate mechanisms and characterize best clinical practice for monitoring reproductive health in men on valproate therapy.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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