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REVIEW ARTICLE

Synthetic neuroactive steroids.

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Summary

This review discusses the topic of synthetic neuroactive steroids. A brief introduction to the mode of action of neuroactive steroids is followed by a short overview of the best-known synthetic neuroactive steroids used in clinical practice and the reasons for their withdrawal from the market. The paper examines various aspects of 6 specific synthetic neuroactive steroids which either have been approved for treatment or are currently in advanced phases of clinical trials, and lists their indications, current experience, and undesirable adverse effects. The authors conclude that the therapeutic potential of neuroactive steroids is still not made full use of. It is to be hoped that this particular class of drugs will find more widespread use also in the management and treatment neurological and psychiatric disorders other than those discussed in this article.

INTRODUCTION

Steroid hormones synthesized *de novo* in the brain and the peripheral nervous system are referred to as neurosteroids. The term neurosteroids was coined in 1981 by Baulieu credited (together with his coworkers) with pioneering work in the field (Corpéchot *et al.* 1981; Baulieu & Robel, 1990; Baulieu *et al.* 1997; Baulieu *et al.* 1998). The new term was intended to differentiate this group of hormones from other glucocorticoids, mineralocorticoids and sex hormones in the circulation (Compagnone & Mellon, 2000). Neuroactive steroids are steroid hormones that act on neurosteroid receptors, regardless of the origin of the steroids.

In terms of their mode of action, neuroactive steroids bind to brain cell receptors activated by γ-aminobutyric acid (GABA), the most abundant inhibitory neurotransmitter in the brain. The GABA-A receptor is also the site where several agents including the benzodiazepines, barbiturates and numerous anesthetics exert their sedative action on the central nervous system (CNS). More details about the GABA-A receptor in terms of its anatomy and pharmacology are available in Ghit *et al.* 2021. Neuroactive steroids can also bind to the receptors for glutamate (N-methyl-D-aspartate, NMDA receptor), the main excitatory neurotransmitter of the human nervous system

(Sedlácek *et al.* 2008). It is through their action on the GABAergic and glutaminergic systems that neuroactive steroids are involved in the control of stimulus transmission within the brain.

From the perspective of pharmacology, the action of neuroactive steroids depends on their levels since, while directly activating the receptors at high doses, low-dose neuroactive steroids augment GABA-A receptor currents. For neuroactive steroids to directly activate a GABA-A receptor, their levels should be > 1μM, a value higher than the physiological range of endogenous neuroactive steroids in the brain (0.1–0.3 μM) (Clarke 1973, Carver & Reddy 2013, Reddy & Rogawski 2002). Nonetheless, the required levels can be obtained and, hence, direct GABA-A receptor activation achieved by exogenous administration of neuroactive steroids (Reddy & Estes, 2016, Lambert *et al.* 1995).

Naturally occurring neuroactive steroids have been assessed in the treatment of epilepsy with fairly consistent outcomes (Herzog *et al.* 2012, Motta *et al.* 2013, Dana-Haeri & Richens, 1983). A definite disadvantage of these neuroactive steroids is their short half-life precluding the use of some in clinical practice; hence the long-standing efforts to replace them with synthetic analogs (Rey & Coirini, 2015).

Based on their chemical structure, endogenous neuroactive steroids are divided into three groups:

a) pregnane neuroactive steroids (allopregnanolone, tetrahydrodeoxycorticosterone [THDOC]);
b) androstane neuroactive steroids (androstanediols, etiocholanone), and;
c) sulfated neuroactive steroids (pregnenolone sulfate and dehydroepiandrosterone sulfate)

Of the positive GABA-A receptor modulators, researchers have to date focused their attention on two progesterone metabolites: allopregnanolone (5α-pregnane-3α-ol-20-one) and its 3-beta isomer – isoallopregnanolone (5α-pregnane-3β-ol-20-one) – found to have antiseizure, anesthetic, anxiolytic and sedative-hypnotic effects (Diviccaro *et al.* 2022).

The overview below examines the synthetic neuroactive steroids formerly/currently used or approved for use in clinical practice, or in advanced phases of clinical trials.

SYNTHETIC NEUROACTIVE STEROIDS

Of the earlier synthetic neuroactive steroids, the best-known ones included hydroxydione, minaxolone, renanolone, and eltanolone (the latter being a 5-beta pregnanolone isomer). Given the low water solubility of pregnanolone, the drug was formulated as a stable emulsion with soybean oil and marketed under the name eltanolone. In clinical trials, eltanolone exhibited fairly good anesthetic properties, which, however, were not superior to those of propofol; moreover, eltanolone had more frequent adverse effects such as involuntary muscle movements (5–10%), myoclonus, and urticaria. Other disadvantages included slower onset of effect, the agent's accumulation and longer recovery time after anesthesia (elimination half-life 0.9–3.5 hours) (Sear, 1998, Tang *et al.* 1997, Hering *et al.* 1996). In late 1995, Pharmacia & Upjohn discontinued a clinical trial because of eltanolone's adverse effects. The trial enrolled a total 1750 patients, with 1% of them developing urticaria.

Hydroxydione (brand names Viadril, Predion, Presuren) was introduced as an anesthetic into clinical practice as early as the 1950s (Lerman 1956). Its most valuable properties included short anesthesia duration, uncomplicated awakening (producing even euphoria in a proportion of patients), and a low incidence of nausea. Hydroxydione use was later discontinued because of frequent and painful phlebitis and thrombosis at the injection site. Phlebitis tended to be more frequent with higher concentrations of hydroxydione solution (1.25%–5%). Lower concentrations required larger volumes of solution and longer infusion times (e.g., it took 2 to 5 minutes to administer 300 ml of solution).

The development of minaxolone (an anesthetic), a most promising agent, was halted on grounds of hepatotoxicity seen after its long-term administration in the rat. A similar fate was experienced by another neuroactive steroid ORG-20599 (an anesthetic), whose development was stopped prematurely. Renanolone, also intended for use as an anesthetic, did not enter clinical practice either; instead, two of its isomers, alfaxolone (also spelled alphaxolone, alfaxalone and alphaxalone) and alfadolone, gained acceptance, see below.

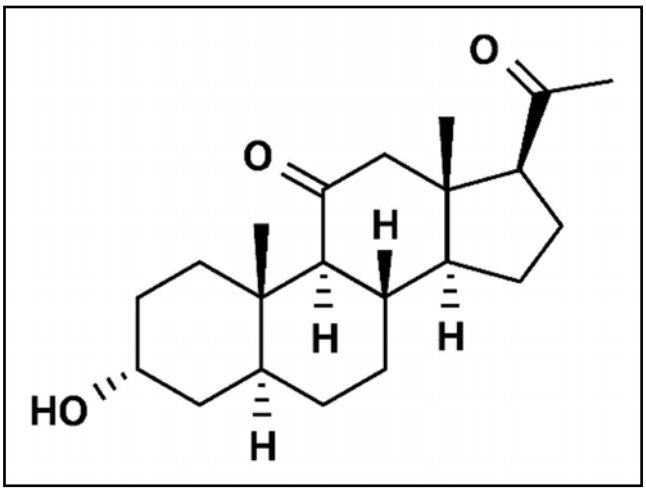

Fig. 1. Alfaxolone (3α-hydroxy-5α-pregnane-11,20-dione)

The anesthetic action of alfaxolone (a synthetic derivative of allopregnanolone) has been known for years (Norberg *et al.* 1999). Alfaxolone is a positive allosteric modulator of the GABA-A receptors, at high concentrations with a direct agonist effect on the GABA-A receptors.

In 1971, researchers at Glaxo formulated an aqueous solution, a mixture of alfaxolone and alfadolone with the addition of Cremophor EL (polyoxyethylated castor oil) as a solvent (brand name Althesin). It was used as an anesthetic in human medicine from 1972 to 1984, when it was withdrawn from the market. The reason for this were frequent hypersensitivity reactions caused by Cremophor EL (Moneret-Vautrin *et al.* 1983), the most frequent culprit in this adverse effect.

An agent with a composition similar to that of Althesin and developed specifically for veterinary practice was Saffan (Schering Plough Animal Health); it was removed from the market in 2002 for its frequent adverse effects. Saffan was formulated such that the mixture contains 9mg/ml of alfaxolone and 3mg/ml of alfadolone. It was later found that alfadolone, while retaining its anesthetic and analgesic activity when administered i.v., would lose its anesthetic effect when administered intraperitoneally with only the analgesic effect persisting (Nadeson & Goodchild 2001). The authors suggested that the difference in alfadolone activity administered intravenously vs. intraperitoneally was due to hepatic metabolism of alfadolone and its conversion to a metabolite possessing an analgesic but not anesthetic effect; hence, alfadolone was removed from the combination. A new alfaxolone-based agent became available in 2001 (Jurox Pty Limited). In 2022, the Australian company was acquired by the US company Zoetis Inc.

Alfaxan, gradually marketed in various countries including the USA, has been used in veterinary practice ever since. It is administered intravenously (USA), with intramuscular administration approved in several countries. The most frequent adverse effects include transient hypotension (15 minutes), hypoventilation, and apnea. In 2018, Jurox successfully introduced a preserved formulation of alfaxolone under the brand name Alfaxan Multidose with pharmacokinetics and pharmacodynamics properties identical with those of Alfaxan and, as approved by the FDA, should be used within 56 days of first puncture.

A new clinical trial of reformulated alfaxolone (brand name Phaxan, Drowbridge Pharmaceuticals) for use in human medicine in Australia. Phaxan is intended for use as an anesthetic in patients undergoing hip joint replacement (Goodchild *et al.* 2020; No author listed 2019). It is an aqueous solution of alfaxolone and 13% betadex (7-sulfobutylether β-cyclodextrin). The clinical trial status (phase III) was changed from recruitment to suspended.

Brexanolone (brand name Zulresso; Sage Therapeutics) is a neuroactive steroid chemically identical with endogenous allopregnanolone. Brexanolone is a positive allosteric modulator of GABA-A receptors, which are pentameric chloride channels. In 2019, it was approved by the FDA as the first synthetic allopregnenolone specifically for the treatment of postpartum depression (Powell *et al.* 2020). It is administered as an infusion lasting 60 hours (2.5 days) with the following dosing schedule (No author listed, 2019):

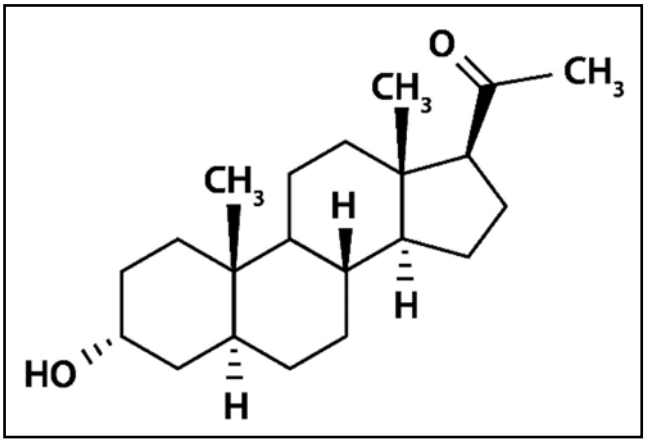

Fig. 2. Brexanolone (3alfa,5alfa-tetrahydroprogesterone)

0–4hrs initial/starting dose 30μg (microgram)/kg/hr
4–24hrs – dose increased to 60μg/kg/hr
24–52hrs – dose increased to 90μg/kg/hr
52–56hrs – dose reduced to 60μg/kg/hr
56–60hrs – dose reduced to 30μg/kg/hr.

Brexanolone's biological half-life is approximately 9 hours. The drug undergoes extrahepatic metabolism, keto-reduction, glucuronidation and sulfation and is excreted through feces and urine. Several clinical trials have documented the beneficial effect of brexanolone (Melzer-Brody *et al.* 2018; Howard *et al.* 2022, Epperson *et al.* 2023). In a group of 26 female patients enrolled in one of the above trials, excessive sedation occurred in only one patient and treatment was successfully completed after 30-minute discontinuation of infusion. Therapy with brexanolone is performed using a special regimen (potential loss of conscience) and the patients should be continuously monitored (at least by a pulse oximeter with alarm) (Faden & Citrome, 2020). The therapeutic effects of brexanolone persisted until day 30 post-infusion. Reported adverse effects included excessive sedation, dizziness, dry mouth, and somnolence. Small amounts of brexanolone pass into breast milk (1–2% of the dose administered). At 36 hours post-infusion, plasma allopregnanolone levels decreased to below 10 ng/ml in 95% of women, with the levels being below the limit of detection (5 ng/ml) at 72 hours in most of the female patients (Leader *et al.* 2019).

Likewise, an analysis of literature data confirmed the efficacy of brexanolone therapy in moderate and severe depression (Balan *et al.* 2023). The exact mechanism of action of brexanolone is unknown; a paper demonstrating brexanolone's anti-inflammatory action through inhibition of toll-like receptors TLRs4 and TLR 7 drew considerable attention.

A disadvantage of brexanolone is its price being approx. USD 34 000 per dose (not including

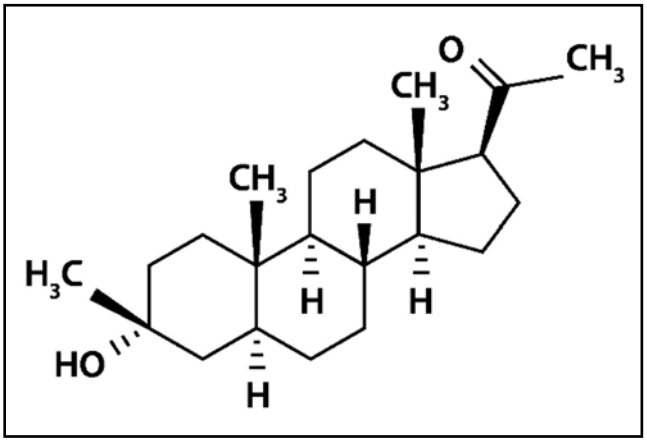

Fig. 3. Ganaxolone (3-hydroxy-3methyl-5-pregnan-20-one)

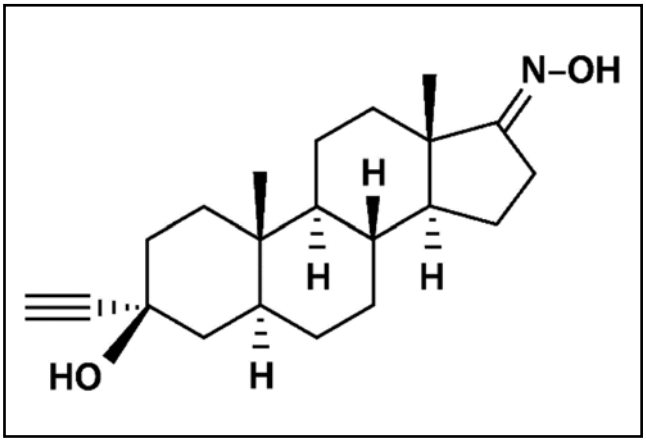

Fig. 4. Golexanolone (GR-3027) (3α-Ethynyl-3β-hydroxyandrostan-17-E-one oxime)

hospitalization costs), that is, about 36 times higher compared with conventional therapy (USD 943) (Shukla *et al.* 2021). Another disadvantage is the lack of data about brexanolone safety and/or other adverse effects reported during long-term therapy. A clinical trial of an oral dosage form of allopregnanolone is currently under way (SAGE-2017). Brexanolone's plasma half-life of 16–23 hours will allow its once-daily administration.

Ganaxolone (Ztalmy, Marinus Pharmaceuticals) is a 3β-methylated synthetic analog of allopregnanolone (a progesterone metabolite). Ganaxolone acts as a positive allosteric modulator of both synaptic and extrasynaptic GABA-A receptors, binding at a site distinct from that of benzodiazepines or barbiturates. By binding to both types of GABA-A receptors, ganaxolone can potentiate both phasic and tonic inhibition. The outcomes of treatment of postpartum depression with ganaxolone have not been convincing and the drug generally failed to meet the expectations. However, researchers were impressed by its antiseizure activity, therefore, it has been and continues to be tested in various types of epilepsy. In the USA, ganaxolone was approved in March 2022 for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients above 2 years of age (Lamb, 2022). The approval was based on the results of the Marigold study, a global phase III clinical trial, where ganaxolone markedly reduced the frequency of major motor seizures versus placebo in children and adolescents with CDD (Kean & Al-Salama 2023; Knight *et al.* 2022). An-initial 6-hour infusion (20 mg/h) was followed by oral administration of ganaxolone (900 mg once daily) for 28 days. While, at lower doses in healthy males (300 mg/day of radiolabeled ganaxolone), the drug exhibited a relatively short half-life in plasma (4 hours), total radioactivity with a half-life of 413 hours suggested extensive

Tab. 1. Overview of synthetic neuroactive steroids already in clinical practice or in an advanced phase clinical trial

Pharmaceutical	Brand name / Manufacturer	Indication	Note
Alfaxolone	Althesin / Glaxo Lab.	Anesthetic	HM
	Saffan / Schering Plough	Anesthetic	VM
	Alfaxan / Jurox Pty Lt.	Anesthetic	VM
	Alfaxan Multidose / Jurox Pty Lt.	Anesthetic	VM
	Phaxan / Phaxtiva / Drawbridge Pharm.	Anesthetic	HM in the stage of clinical testing
Brexanolone	Zulresso / Sage Therapeutics	Postpartum depression	HM
Ganaxalone	Ztalmy / Marinus Pharmaceuticals	Seizures in CDKL5 deficiency disorder	HM
Golexanolone	GR 3027 / Umecrine Cognition	Treatment of hepatic encephalopathy and symptoms of Parkinson's disease	HM
Sepranolone	UC1010 / Asarina Pharma AB	Premenstrual dysphoria	HM
Zuranolone	SAGE-217 / Sage Therapeutics	Major depressive disorder and postpartum depression	HM

Abbreviations: HM – human medicine; VM – veterinary medicine

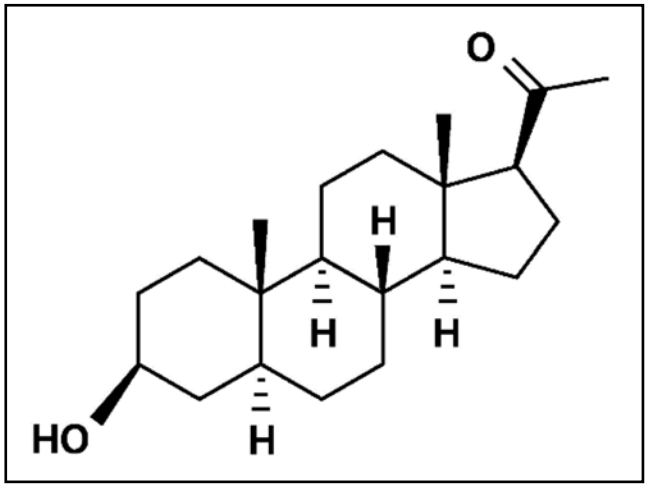

Fig. 5. Sepranolone (3β-Hydroxy-5α-pregnan-20-one)

metabolism to long-lived metabolites (Fitch *et al.* 2023). Ganaxolone thus became the first drug and an innovative therapeutic approved by the FDA specifically for this condition. Ztalmy is also being tested in other conditions such as PCDH19 gene-related epilepsy, tuberous sclerosis, and refractory status epilepticus. The drug may cause serious adverse effects including somnolence and sedation as well as suicidal behavior and ideation. Other frequent adverse reactions include fever, excessive salivation, and seasonal allergy.

Golexanolone is a GABA-A receptor-modulating steroid antagonist (Stromberg *et al.* 2015; Wetten *et al.* 2022; Johansson *et al.* 2015). Reduced activation of GABA-A receptors by golexanolone reduces peripheral inflammation and neuroinflammation while improving cognitive and motor functioning in hyperammonemic rats.

The documented therapeutic effects are believed to also occur in patients with hepatic encephalopathy and, possibly, other conditions associated with neuroinflammation.

While selectively antagonizing the stimulatory activity of some neuroactive steroids such as allopregnanolone and tetrahydrodeoxycorticosterone (THDOC) on the GABA-A receptor, golexanolone has no direct effect on the activation of the GABA-A receptor by GABA. Golexanolone binds to allosteric sites of the GABA-A receptor to modulate and open chloride ion channels resulting in hyperpolarization thereby inhibiting neurotransmission, which reduces the likelihood of successful depolarization.

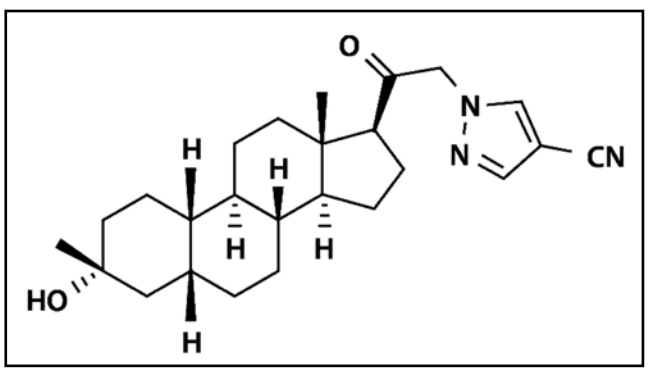

Fig. 6. Zuranolone (3β-Methyl-21-(4-cyano-1*H*-pyrazol-1'-yl)-19-norpregnanolone)

Golexanolone is a neuroactive steroid currently undergoing clinical trials for several diagnoses, in particular hepatic encephalopathy and hypersomnia. While, in experiment, golexanolone clearly improved cognitive and motor functioning in hyperammonemic rats (Mincheva *et al.* 2022); the improvement was less marked in a small clinical trial where it did not differ statistically from that seen in a control group (Montagnese *et al.* 2021).

In early 2023, golexanolone was granted orphan drug designation status for the treatment of primary biliary cholangitis in the USA. A preclinical trial assessing golexanolone in the treatment of Parkinson disease and a Phase II clinical trial investigating the molecule's safety and tolerability, pharmacokinetics and preliminary efficacy in primary biliary cholangitis are currently under way.

Sepranolone (also isopregnanolone, isoallopregnanolone, epiallopregnanolone), an endogenous progesterone metabolite, is a negative allosteric GABA-A receptor modulator. If bound to the GABA-A receptor, sepranolone antagonizes the effect of allopregnanolone. The drug has been tested in the treatment of premenstrual dysphoric disorder (PMDD) and is currently used in patients experiencing PMDD-related mood symptoms. In a study focused on sepranolone pharmacokinetics, 75% of patients reported subjective improvement after sepranolone compared with only 47% of patients after placebo (Bixo *et al.* 2017).

The safety of therapy with sepranolone was demonstrated in a multicenter clinical study enrolling 206 female patients (Backström *et al.* 2021). Sepranolone was administered subcutaneously at doses of 10 or 16 mg every 48 hours starting 14 days prior to onset of menstruation. Quite surprisingly, the clinical effect was better with the lower dose and, also, the plasma levels of sepranolone were similar with both doses or only somewhat higher with the 16 mg dose. The most frequent adverse effect was pain at the injection site, which was also the most common reason for termination of therapy. However, the outcomes of sepranolone therapy did not differ from that with placebo and the beneficial effect of sepranolone was ascribed to the placebo effect. A clinical trial is currently under way investigating the use of sepranolone in the treatment of premenstrual migraine and Tourette syndrome. Regarding the latter condition, a marked beneficial effect of sepranolone was observed already in an experimental murine model of Tourette syndrome (Cadeddu *et al.* 2020).

Zuranolone (SAGE-217/BIIB125) is another neuroactive steroid acting as a positive allosteric GABA-A receptor modulator (Powel *et al.* 2020, Reddy & Rogawski 2002, Althaus *et al.* 2020, Kaufman *et al.* 2022). Chemically, it is an oral dosage form of allopregnanolone. The drug was developed by Sage Therapeutics and Biogen Inc. announcing, in late 2022, the completion of the multistep process of new drug application (NDA) for zuranolone to the FDA. The indications for zuranolone therapy include major depressive disorder (MDD) (Clayton *et al.* 2023) and postpartum depression (PPD) (Deligianidis *et al.* 2021).

Clinical trials showed zuranolone is a fast-acting drug, with an advantage being its oral administration. It is administered once daily at doses of 30–50 mg for 2 weeks in adults with MDD and PPD. In the process of clinical development, zuranolone has to date shown quick and permanent reduction of depressive symptoms with a generally well-tolerated and consistent safety profile. The most frequent adverse effects include sleepiness, headache, and dizziness.

FUTURE POTENTIAL AREAS OF NEUROACTIVE STEROID USE

Over the years, numerous pharmaceuticals possessing well-characterized neuroactive steroid properties, that is sedative-hypnotic, anesthetic, anxiolytic and anticonvulsive effects, have been and are being introduced into clinical practice. It has turned out that the therapeutic potential of neuroactive steroids is much greater than anticipated. It has been suggested they might find use in the management of stroke and its complications ((Xu *et al.* 2022, Andrabi *et al.* 2022; Marek *et al.* 2022); neuropathic pain (Meyer *et al.* 2019), treatment of neurodegenerative diseases (Akwa, 2022), retinal injury (Izumi *et al.* 2023), and other conditions. Sulfated dosage forms of pregnanolone and allopregnanolone have been shown to exert an inhibitory effect on the NMDA receptor and could possibly have a beneficial effect on memory (Gunay & Pinna 2022). Another potential area of neuroactive steroid use is the management of some disorders already prenatally and early after birth, still in the realm of experimental medicine (Sze & Brunton, 2022; Sze & Brunton 2021).

CONCLUSION

Synthetic neuroactive steroids have eliminated the crucial disadvantage of their endogenous counterparts, that is, a short half-life, thus paving the way to their use in clinical practice. The largest body of clinical experience with neuroactive steroids comes from their use in anesthesia. Neuroactive steroids are expected to make anesthesia as gentle as possible, particularly in pediatric patients. Novel neuroactive steroid formulations, both those mentioned in this review and others approved for other indications, open a new era of synthetic neuroactive steroid use in clinical practice. Experts have little doubt about their great potential in the treatment of other neurological and psychiatric disorders as discussed above.

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