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Review Article

Gepirone: A Current Breakthrough to Antidepressant Outgrowth

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ABSTRACT

Major depressive disorder (MDD) has been a persistent challenge in the field of mental health. Several drugs in past have been used to treat mental illness with noticeable emotional depression. Gepirone is a promising medication for patients combating with MDD. FDA approved gepirone in September 28, 2023 under brand name Exxua as a novel antidepressant drug to be a possible substitute to selective serotonin reuptake inhibitors (SSRIs). Gepirone does not belong to selective serotonin reuptake inhibitors (SSRI), however it still works by activating certain serotonin receptors. Gepirone ER (Exxua) is an efficacious medication in the treatment of mental health of patients. Exxua is to be used with cautious as it can cause QT prolongation resulting in arrhythmias which may be life threatening. The drug poses new vision to other treatment options available in market. The significant stage in development of the drug will assist researchers, physicians and regulatory bodies to be aware of the challenges pertaining to mental health and improving treatment options. The present review presents critical view on gepirone (Exxua) to pharmacists and physicians as a new treatment option of mental illness.

INTRODUCTION

Major depressive disorder (MDD) is a syndrome, which is a serious health concern in global populations. MDD critically suppress psychological functioning and depletes common human life. A global survey revealed that almost 350 million people suffer from this neuropsychiatric disorder and WHO forecasted this disease to stand first in 2030 [1,2]. A number of currently available antidepressants may improve the quality of mental health, however new developments are required from clinical aspects. It is nowadays need to gain awareness of the properties of new forthcoming drugs for

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efficacious and targeted treatment of depressive disorders [3]. Gepirone (EXXUA) an analog of buspirone after a milestone was approved by FDA in September 28, 2023 as a novel drug for treating MDD[4]. The drug is non-sedative and is lacking anticholinergic activity and has low levels of potential for misuse [5]. The review aims to throw light upon gepirone and provides ample of information for researchers, psychiatrists, pharmacologist and other mental healthcare professionals to treat MDD.

Drug description

Gepirone an analogue of buspirone is orally available antidepressant. The drug was initially synthesised by Bristol-Myers Squibb in 1986 and is marketed by Fabre-Kramer Pharmaceuticals under the brand name Exxua in September 2023. The drug having molecular formula $C_{19}H_{29}N_5O_2$ is off white to pale yellow solid. The 2D and 3D structures of gepirone are shown in Fig.1 and Fig. 2 and its synthetic route is explained in Fig. 4 [6].

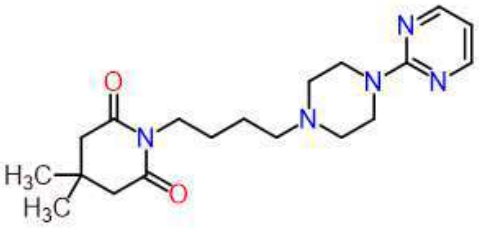

Fig. 1: 2D structure

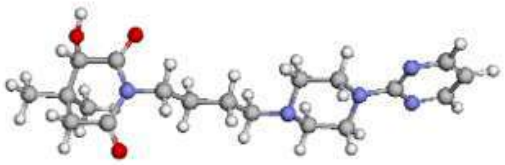

Fig. 2: 3D structure

IUPAC Name: 4, 4-Dimethyl-1-(4-(4-(pyrimidin-2-yl) piperazin-1-yl) butyl) piperidine-2,6-dione The structure activity relationship (SAR) rationalizes that in buspirone moiety the five membered ring is substituted by two methyl groups. Replacement of one of the methyl group results in inactive molecule. Substitution of ethyl groups in place of both methyl groups decreases the efficiency of the drug. Kaduk et. al[7] reported the crystal structure of gepirone showing separate molecules in absence of classical hydrogen bonds, however intra and inter molecular C-H---N and C-H---O bonds exists. Each of the bond distances, bond angles, and torsion angles are within normal ranges obeying Mercury Mogul Geometry check [8]. The computational parameters are presented in Table-1.

Table-1. Computational Parameters of Gepirone

S. No.	Physicochemical properties	Values
1.	Melting point	106-108 °C
2.	Density	1.14 ± 0.06 g/cm^{-3} (20°C)
3.	Monoisotopic mass	395.2088029
4.	Hydrogen Bond Donor Count	0
5.	Hydrogen Bond Acceptor Count	6
6.	Topological Polar Surface Area	69.6 Å^2
7.	Solubility	Practically insoluble in water, but very soluble in dichloromethane, methyl and ethyl alcohol
	Water Solubility	1.09 mg/mL
8.	Log P	2.09
9.	Polarizability	40.92 Å^3
10.	Refractivity	101.49 m^3·mol^{-1}
11.	Elemental Analysis	Elemental Analysis: **C**,63.48; **H**,8.13; **N**,19.48; **O**,8.90

12.	m/z ratio	359.23 (100.0%), 360.24 (20.5%), 361.24 (2.0%), 360.23 (1.8%)
13.	Optical Activity	Achiral

Data obtained from Chembook[9], PubChem[10] and Drug Bank Online[11]

Historical development of Gepirone

The milestone growth of gepirone extends backward to period of 20 years (1984) with almost a dozen of clinical trials to prove its efficacy. Initially Fabre-Kramer in 1993 obtained gepirone, in 1998 the licence was relocated to organon. After phase 3 clinical trials, the first report was submitted to FDA in 2001, a second report was submitted in 2003 showing relapse in patients with depression resulting gepirone to be ceased. The licence was taken back by Fabre-Kramer pharmaceuticals Inc. in 2005. In 2007, new finding in collaboration with GlaxoSmithklein was submitted to FDA which was not accepted. Kramer challenged this decision in 2012 which was heard by FDA psychopharmacologic drug advisory committee in 2015. The company submitted fresh application with more findings in 2022 which was finally approved in 2023 [12]. The chronological development of Exxua is presented in Fig 3 [13,14].

Fig. 3: Chronological development of Exxua

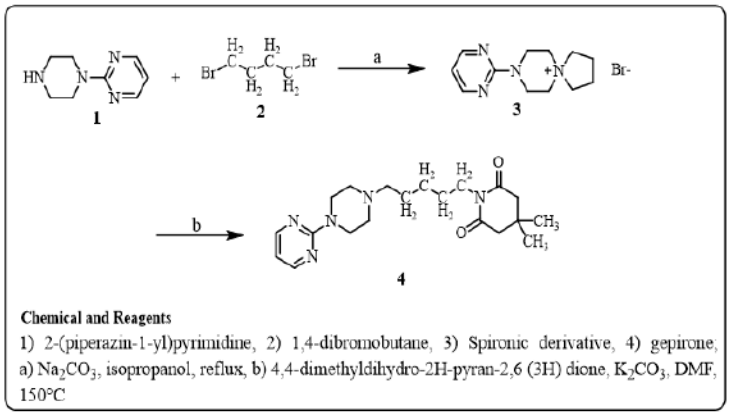

Fig. 4: Synthetic route for gepirone

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic (ADME) studies of gepirone (Exxua) show linear and dose proportionate properties in range of 18.2-72.6 mg. The bioavailability of the drug is 14% to 17% after oral absorption and attains maximal plasma concentration (C_{max}) within 6 hours. Absorption also depends upon the amount of fat content in food. The distribution volume is around 94.5 L, normally 72% of the drug binds to in-vitro plasma protein and is eliminated nearly in 5 hours. The drug is metabolized by the enzyme CYP3A4 to major metabolites (3'-OH and 1-PP) which are present in higher concentration than the present drug. Generally, 60% of the drug is cleared through urine within 24 hours. The pharmacodynamics properties is linked to gepirone and its active metabolites (3'-OH and 1-PP) which binds to $5HT_{1A}$ receptors and α_2 receptors respectively. This causes increase in QT interval in individuals kept on treatment, therefore patients need to have normal electrolyte balance and ECG monitoring before the start of treatment [15,16].

Mechanism of Action

The mechanism of action of gepirone (Exxua) is still undefined, however it may be involved to its regulation of serotonin level in brain through selective agonist action of $5HT_{1A}$ receptor. Major depressive disorder (MDD) occurs as a result of disorder of this receptor and decrease in $5HT_{1A}$ binding. Exxua functions as an important selective agonist of the $5HT_{1A}$ receptor in controlling mood and anxiety, it may also increases receptor signalling and serotonergic transmission to improve major symptoms of depression. The drug also acts as an antagonist at $5HT_{2A}$ receptor present in the central nervous system, which is responsible for knowledge and thought. Abnormal activity of $5HT_{2A}$ receptor results in several CNS disorders such as psychiatric, schizophrenia and depression. Exxua by function as $5HT_{2A}$ antagonist possess both antipsychotic and antidepressant activity. Gepirone hydrochloride is found to be too selective medication in comparison to the available antidepressants which act as a selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs). In case serotonin 1A receptor is triggered, the flow of serotonin is reduced resulting in enhancement of mood and improvement in mental health of individuals [17,18]. The mechanism of action is shown in Fig. 5.

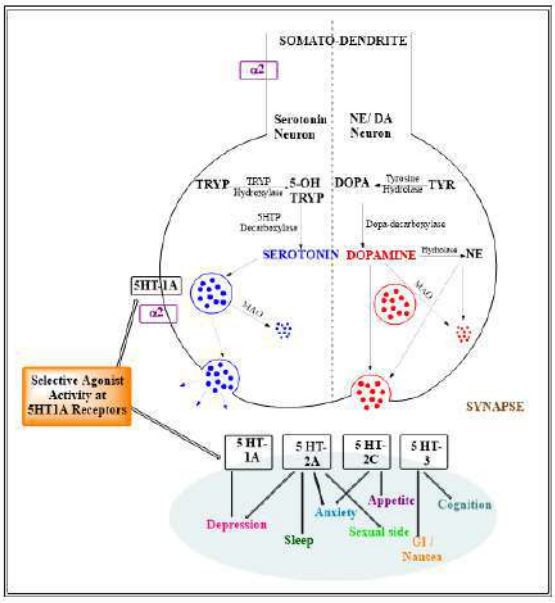

Fig. 5: Mechanism of action of selective agonist drugs (gepirone) at $5HT_{1A}$ receptors

(TRYP = tryptophan; TRYP Hydroxylase = Tryptophan hydroxylase; 5-OH TRYP = 5-hydroxy tryptophan; NE = Norepinephrine; DA = Dopamine; MAO = Monoamine oxidase; $5HT_{1A}$ = 5-hydroxytryptamine receptor 1A; GI = Gastrointestinal)

Side effects

Gepirone is tolerated well and has superior efficacy on oral administration. There are certain side effects which includes: headache, tiredness, insomnia, dizziness, nausea, vomiting, indigestion, diarrhoea, respiratory tract infection. Medical care is to be sought in case of serious side effects such as fast or irregular heartbeats, shortness of breath, sudden loss of vision, loss of coordination, tremors, profuse sweating and unsteady feeling [19].

Computational Analysis

The gepirone structure was predicted by ^{1}HNMR and ^{13}CNMR chemical shifts using Chem Draw Professional ACS Document1996. All the values supported the structure of the molecule Fig. 6 and Fig. 7.

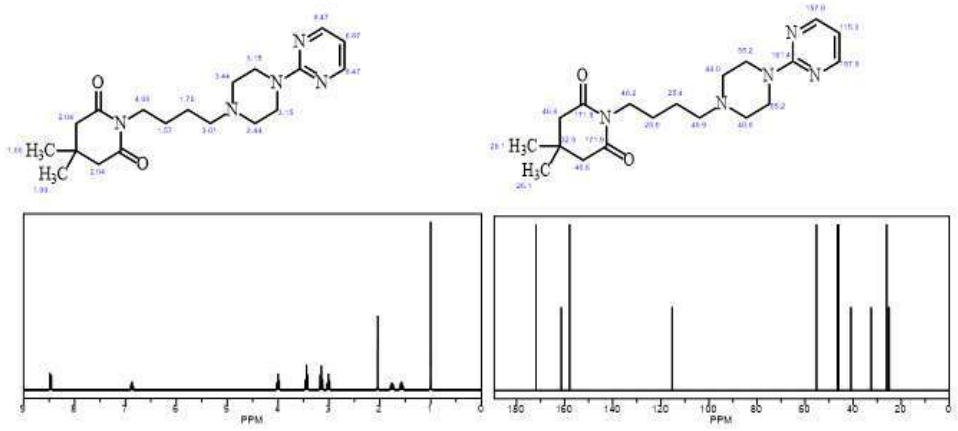

Fig. 6: ChemNMR ^{1}H Estimation **Fig. 7: ChemNMR ^{13}C Estimation**

Effect On Cardiac Electrophysiology

Gepirone upon oral administration can result in changes in heart rhythm called QT prolongation. This causes fluctuations in heartbeat and may cause chest pain, dizziness and breathing trouble. The increase in risk of potentially life threatening cardiac arrhythmia has been reported by use of gepirone. Patients with congenital long QT syndrome are contraindicated to gepirone, however regular ECG has to be done on them before the start of treatment and also in those who develop QT_c > 450 m sec. It is advised not to increase the dose of gepirone rapidly if QT_c > 450 m sec and the dosage to be reduced when used along with moderate CYP3A4 inhibitors [20, 21].

Global Market Prediction

The antidepressant market is promptly growing as a result of increasing occurrence of depression and other mental health disorders globally. The rise in frequency of market is associated to increase in awareness among people for depressive disorder. Medicines both generic and patented brands are marketed across the developed and developing countries. The prediction of global antidepressant market has been valued as USD 10.15 billion, though in 2024 it grew to USD 11 billion. Overall the assessment year span (2024-2034) it is anticipated to gain a CAGR of 5.2% and outstretch to a value of USD 18.3 billion [22].

Brief Review on Gepirone Formulations

The antidepressant potential of gepirone to combat increasing global disorder is only as an extended-release formulation [6]. Gepirone ER was initially evolved in the form of an immediate release (IR) formulation, thereafter the ER formulation was considered to have more therapeutic advantages than the IR formulations which was discarded. Hydroxypropyl methylcellulose present as a active

ingredient in ER formulation helps absorption by 16 hours and is administered once a day. Research on pharmacological and clinical trials on gepirone ER and immediate release formulations have supported the fact that the ER formulations were better tolerated and had significant activity as compared to gepirone IR formulations [23]. Gepirone-ER was found to be efficacious and well tolerated when its potency was examined versus placebo in patients for short term treatment of MDD [24]. Gepirone-ER has been reported to be an efficient and well tolerated formulation for patients with high grade anxious depression [25]. The extended release formulation of gepirone remarkably reduces the symptoms in patients with severe illness of depression [26]. The safety profile and tolerability of gepirone-ER formulation is considered to be one of the most important options for patients who do not respond to the first line antidepressant therapy[27]. The pharmacokinetic studies on gepirone immediate-release and extended-release formulations on comparison showed that the 1-(2-pyrimidinyl)-piperazine (1-PP)metabolite, C_{max} and AUC_{30} possessed statistically significant higher value ($P<0.05$) whereas the Tmax value was found to be lower in case of gepirone-IR as compared with ER formulation [28].

Future Prospects

The future of Exxua promises progressive results in patients with MDD and may open new possibilities in the treatment of resistant depression. Inspite of being recently developed drug, further researchers are required to affirm its novelty. Exxua is likely to retain its assurance to patients and it will be of great interest to see the drug in maintaining its role in treatment of MDD. The increase in demand will depend upon its positive outcomes which will influence its market value. The enhance requirement for gepirone is anticipated to undergo remarkable hike during upcoming years. The stable growth of gepirone global market in subsequent years will determine its future outlook. However, market dynamics may be effected by competing constraints and firm regulations.

CONCLUSION

Gepirone, an analogue of buspirone is a new option with major depressive disorder. Exxua (gepirone) is found to have a key role in controlling mood and anxiety. Despite being a new drug, there are challenges to it specially for QT prolongation in patients. Therefore, further studies are required to establish its novelty. This article will also benefit researchers in investigating role of $5HT_{1A}$ receptor in depression and psychiatric disorders. The awareness of pharmacological effects of the drug will pave way for physicians to establish a suitable reasoning to prescribe this medication.

Conflict Of Interest

The authors declare there is no conflict of interest in publishing the article.

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