Announcing the novel class of GABA–A receptor selective positive allosteric modulator antidepressants

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“The novel class of GABA–A receptor selective positive allosteric modulator antidepressants (GASPAMAs) has brought forth significant improvement and positive impact to the management of patients with depression disorders in clinical practice”

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The majority of currently available clinical antidepressant drugs increases serotonergic, noradrenergic and/or dopaminergic neurotransmission in the central nervous system (CNS) [1–3]. These currently available antidepressants exhibit their unique pharmacological activities by 14 different distinct pharmacological mechanisms of actions [1–9]. Presently, 11 of the 14 different classes of antidepressants accomplish their pharmacological actions by blocking one or more of the reuptake transporter pumps and/or blocking some certain specific subtype of receptors for any of the three monoaminergic (i.e., serotonergic/noradrenergic/dopaminergic) neurotransmission systems [1–3]. The 12th class inhibits the enzyme monoamine oxidase [1–3], the 13th class works by blocking the *N*-methyl-D-aspartate (NMDA) glutamatergic ionoreceptor [1–5], while the 14th class works by acting as a GABA–A receptor selective positive allosteric modulator antidepressant (GASPAMA) [5–9].

The novel class of GABA–A receptor selective positive allosteric modulator antidepressants (GASPAMAs) has brought forth significant improvement and positive impact to the management of patients with depression disorders in clinical practice [5–9]. There are growing body of evidences that the extrasynaptic sites gamma aminobutyric acid (GABA) neurotransmission system (mediated via extrasynaptic GABA–A receptors on the glutamatergic principal neurons) at the cortical and subcortical neuroaxes play a major central role in the pathogenesis of depressive disorders most especially postpartum depression disorder (PPD) and certain neuropsychiatric condition such as premenstrual dysphoric disorder (PMDD), respectively [5–9].

Regarding PPD; it has been implicated that a sudden drop in the plasma level of progesterone hormone following parturition will unavoidably lead to a corresponding decrease in the level of allopregnanolone neuroactive steroid in the entire CNS, because the placenta synthesizes the vast majority and substantial amount of the progesterone hormone secreted during the late first trimester, entire second trimester and third trimester of pregnancy period. So, during the postpartum period, there is a drastic reduction in the levels of both progesterone hormone and allopregnanolone neuroactive steroid as a result of placenta extrusion during parturition process [5–9].

Concerning PMDD; it has also been implicated that a rapid decline in the plasma level of progesterone hormone after the usual peak period on the 21st day post-last menstrual period following ovulation occurrence in the absence of fertilization/conception will unavoidably lead to a corresponding decrease in the level of allopregnanolone neuroactive steroid in the entire CNS, because the ovarian corpus luteum synthesizes the vast majority and

substantial amount of the progesterone hormone secreted during the luteal phase of menstrual cycle period. So, during the last/late second-half of the luteal phase of menstrual cycle period that commences at the end of 21st day post-last menstrual period till the appearance/manifestation of endometrial shedding with accompanied menstrual flow occurrence; there is a drastic reduction in the levels of both progesterone hormone and allopregnanolone neuroactive steroid as a result of ovarian corpus luteum degeneration to form ovarian corpus albicans (that is, luteolysis process) during this late premenstrual flow occurrence period [5–9].

These aforementioned decrease in the level of allopregnanolone neuroactive steroid in the entire CNS during the postpartum period or during the last/late second-half of the luteal phase of menstrual cycle period in the absence of fertilization/conception will definitely result in abrupt withdrawal effect with disinhibition of the extrasynaptic GABA–A receptors located on the glutamatergic principal neuron projections at the prefrontal cortex and the hippocampal region. The malfunctioning of these glutamatergic neurotransmission circuit projections at the prefrontal cortex or hippocampal region seems to alter mood and affect control, thereby leading to depressive or anxiety state, respectively [5–9]. There are substantial evidences that GABA neurotransmitter is critically involved in the regulation of neural plasticity, resilience and neurogenesis [5–9]. The available evidences suggest that depressive disorders are significantly associated with the dysfunctional loss of efficient extrasynaptic sites GABAergic neurotransmissions inhibiting the glutamatergic principal neurons at the cortical and subcortical neuroaxes (i.e., prefrontal cortex and hippocampus); and that effective antidepressant therapy with a GABA–A receptor selective positive allosteric modulator antidepressant (GASPAMA) will increase extrasynaptic sites GABAergic neurotransmission activity, neurogenesis and synaptic connectivity across these cortical and subcortical areas [5–9]. The new class of GABA–A receptor selective positive allosteric modulator antidepressants (GASPAMAs) comprises of rapid-onset antidepressants that include novel agents such as brexanolone (also known as allopregnanolone) [8–14], zuranolone (SAGE-217 or S-812217) [8,9] and ganaxolone (CCD-1042) [5–9,15–18]. GASPAMAs have been postulated to act via positive allosteric modulation or selective activation of the allopregnanolone neuroactive steroid-allosteric binding sites localized in the extrasynaptic GABA–A receptors found on glutamatergic principal neurons at the prefrontal cortex or hippocampal neuroaxis to mediate antidepressant or anxiolytic effect, respectively. These extrasynaptic GABA–A receptors containing especially delta (δ) subunits for GASPAMA binding sites (delta [δ]-GABA-A-PAMAs) exhibit the greatest potentiation in the cortical and subcortical areas involving the prefrontal cortex and hippocampus (that is, restricted brain localization), which mediate their antidepressant and anxiolytic actions, respectively; perhaps through extrasynaptic GABA–A receptor-dependent increase in coherent neuronal circuit activities with the enhancement of GABAergic inhibitory extrasynaptic potential (GABAergic IESP) output on the glutamatergic excitatory principal neurons projecting across the prefrontal cortex or hippocampal neuroaxis to mediate antidepressant or anxiolytic effect, respectively [5–9]. Furthermore, GASPAMAs bind to the allopregnanolone neuroactive steroid-allosteric binding sites of the extrasynaptic GABA–A receptors to positively modulate and open the chloride ion conduction channels, thereby resulting in the membrane hyperpolarization/hyperconduction process associated with persistent chloride anion flux through the extrasynaptic GABA–A receptors containing especially delta (δ) subunits for GASPAMA binding sites (delta [δ]-GABA-A-PAMAs) that will result in the inhibition of glutamatergic neuronal excitation firing activities. This causes inhibitory effect on glutamatergic neurotransmission activities, and thereby reducing the chance of successful action potentials (depolarization) from occurring/generating [5–9].

Also, allopregnanolone has recently been found to be an agonist of the newly discovered membrane progesterone receptors (mPRs), including mPR δ , mPR α and mPR β , with its activity at these receptors about a magnitude more potent than at the GABA–A receptor [8–14]. The action of allopregnanolone at these aforementioned mPRs may be related, in part, to its neuroprotective and antigonadotropic properties [8–14].

Allopregnanolone is an endogenous inhibitory pregnane neuroactive steroid. It is biosynthesized from progesterone *denovo/in vivo*. The biosynthesis of allopregnanolone in the brain starts with the conversion of progesterone into 5 α -dihydroprogesterone by 5 α -reductase type I enzyme. After that, 3 α -hydroxysteroid dehydrogenase converts this intermediate into allopregnanolone. Allopregnanolone in the brain is produced by cortical and hippocampus pyramidal neurons and pyramidal-like neurons of the basolateral amygdala [8–14].

Regarding biological functions, allopregnanolone and its other synthetic structural congeners such as zuranolone (SAGE-217 or S-812217) and ganaxolone (CCD-1042) possesses a wide array of effects, including, in no particular order: antidepressant, anxiolytic-sedative, anticonvulsant, stress-reducing, rewarding, prosocial, antiaggressive, prosexual, sedative, prosleep, cognitive, memory-impairment, analgesic, general anaesthetic, neuroprotective and neurogenic effects [5–14]. Fluctuations in the levels of allopregnanolone and the other neurosteroids seem to play an important role in the pathophysiology of mood, anxiety, PMDD, premenstrual syndrome, catamenial epilepsy and

various other neuropsychiatric conditions [5–14]. During pregnancy, allopregnanolone and pregnanolone are involved in sedation and anesthesia of the fetus [5–14]. In fact, the novel class of GASPAMAs is the first class of antidepressant agents with the all in one combine pharmacologic properties of antidepressant, anxiolytic-sedative, anticonvulsant and general anesthetic effects in each of its member agents [5–14].

Brexanolone (allopregnanolone) [8–14] is a neurosteroid that has recently been approved by the US FDA in the year 2019 for used in the treatment of only PPD via intravenous infusion over a 60-h period under thorough medical supervision because of the risk of severe sedation, hypnosis, loss of consciousness and profound respiratory arrest. The commercial sales began in June 2019. The long hours of administration time, as well as the cost of US\$34,000, have raised concerns about accessibility for many women with PPD [8–14]. While zuranolone (SAGE-217 or S-812217) [8,9] and ganaxolone (CCD-1042) [5–9,15–18] are presently still undergoing clinical trial for the treatment of PPD and major unipolar depression disorder (MDD) [5–9,15–18]. Also, these GASPAMAs will likely be effective for the treatment PMDD too; but clinical trials are yet to be conducted on this neuropsychiatric condition using any of these highlighted GASPAMA agents [5–14]. Ganaxolone (CCD-1042) is administered intravenously [5–9,15–18]. Zuranolone (SAGE-217 or S-812217) was developed as an improvement of allopregnanolone (brexanolone) with high oral bioavailability and a biological half-life suitable for once-daily administration [8,9]. As of October 2019, zuranolone is in Phase III clinical trials for MDD, PPD and insomnia and is in Phase II clinical studies for bipolar depression, essential tremor, and Parkinson's disease [8,9]. It is also in the preclinical trial stage for dyskinesias [8,9].

At this junction, we want to emphatically reiterate from the clinical psycho-neuropharmacologic point of view that these novel GASPAMAs [5–14] will likely be of more immense benefit for females with PPD or females with MDD or females with PMDD than male counterparts with MDD because of the different fluctuating levels of endogenous allopregnanolone neurosteroid influence and the varied expressions of extrasynaptic GABA-A receptors containing particularly the delta (δ) subunits having allopregnanolone neuroactive steroid-allosteric binding sites localized on them during the pregnancy–postpartum phase period or follicular–luteal phase of menstrual cycle period; as males do not biosynthesize physiologically significant neuroactive levels of endogenous allopregnanolone neurosteroid [5–14]. This gender-based benefit will likely be applicable to the observed anxiolytic-sedative, anticonvulsant and general anaesthetic effects of the GASPAMA agents too [5–14].

Conclusion

In conclusion, based on these evidences of interference with the extrasynaptic sites GABAergic neurotransmission system located on the glutamatergic principal neurons, it has become imperative to reaffirm and substantiate the GABAergic deficit hypothesis of depression disorders previously postulated and proposed by Luscher *et al.*; as obviously revealed by the described mechanism of action for the GASPAMA agents [19].

Update on the current antidepressants classification nomenclature

Fasipe classified antidepressant agents based on their different unique pharmacologic mechanisms of actions. Currently, the updated version for the various classes of clinically available antidepressants include [1–14]:

- Tricyclic antidepressants (TCAs) such as amitriptyline, imipramine, desipramine, nortriptyline, clomipramine, trimipramine, protriptyline and doxepin.
- Monoamine oxidase inhibitors (MAOIs) such as phenelzine, nialamide, isocarboxazid, hydracarbazine, tranylcypromine, moclobemide, *bifemelane, *pirlindole, *toloxatone, *selegiline, *rasagiline and *safinamide.
- Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, paroxetine, citalopram, escitalopram and fluvoxamine.
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, desvenlafaxine, duloxetine, *ansofaxine, *nefopam and *levomilnacipran.
- Norepinephrine-dopamine reuptake inhibitor (NDRI) such as bupropion.
- $\dagger\dagger$ Selective norepinephrine reuptake inhibitors (NRIs) such as *reboxetine, *atomoxetine, *viloxazine and *teniloxazine (also known as sulfoxazine or sufoxazine).
- Serotonin receptors antagonist with serotonin reuptake inhibition (SARI) such as trazodone, nefazodone and *vortioxetine.
- $\dagger\dagger$ Serotonin 5-HT_{1A} autoreceptor partial agonist with serotonin reuptake inhibition (SPARI) such as *vilazodone
- Noradrenergic α_2 -receptor antagonist with specific serotonergic receptors-2 and -3 antagonism (NASSA) such as mirtazapine and [®]mianserin.

- †† Norepinephrine reuptake inhibitor with serotonin receptors antagonism (NRISA) such as maprotiline.
- †† Serotonin-norepinephrine reuptake inhibitor and serotonin receptors antagonism antidepressant with potent antipsychotic dopaminergic D₂ receptor blockade/antagonism (SNRISA with potent antipsychotic dopaminergic D₂ receptor blockade/antagonism) such as amoxapine.
- †† Atypical antipsychotics that exhibit potentially strong serotonergic 5-HT_{2A/2C} receptor blockade with or without dopaminergic D₂ receptor weak antagonism/partial agonism such as *asenapine, *paliperidone, *sertindole, *ziprasidone, *zotepine, *amisulpride, *sulpiride, *cariprazine, *olanzapine, *quetiapine, *clozapine, *risperidone, *lurasidone, *aripiprazole, *brexpiprazole and *pimavanserin.
- †† *N*-methyl-D-aspartate (NMDA) glutamatergic ionoceptor blockers that exhibit a direct action on the excitatory glutamatergic neurotransmission system such as *ketamine, *CP-101,606 (traxoprodil), *GLYX-13 (rapastinel), *NRX-1074 (apimostinel) and riluzole.
- †† GABA–A receptor selective positive allosteric modulator antidepressants (GASPAMAs) such as *brexanolone (also known as allopregnanolone), *zuranolone (SAGE-217 or S-812217) and *ganaxolone (CCD-1042).
- § Melatonergic MT₁ and MT₂ receptors agonist with selective serotonergic 5-HT_{2B} and 5-HT_{2C} receptors antagonism (MASSA) class such as ‡agomelatine.

NOTE: †† Emerging antidepressant classes using mechanisms of action based classification [1–14];

* Novel/emerging antidepressant drug(s) in a particular class [1–14];

® Drug approval was rejected/denied by the FDA due to the submission of fraudulent data regarding its clinical trial by the investigators but had been approved for the treatment of depression disorders long time ago in the European Union and other countries [1–3];

§ MASSA has not been universally accepted as an antidepressant class as there are controversies over it [2,3];

‡ Agomelatine has not been universally accepted as an antidepressant agent as there are controversies over it [2,3].

Furthermore, the new justifiable antidepressant classes [1–14] are selective norepinephrine reuptake inhibitors (NRIs), serotonin 5-HT_{1A} autoreceptor partial agonist with serotonin reuptake inhibition (SPARI), atypical antipsychotics, NMDA-glutamatergic ionoceptor blockers and GABA–A receptor selective positive allosteric modulator antidepressants (GASPAMAs). While the class being referred to as melatonergic MT₁ and MT₂ receptors agonist with selective serotonergic 5-HT_{2B} and 5-HT_{2C} receptors antagonism (MASSA) class, that presently has agomelatine as the only member agent remains a paradoxical class that does not fit appropriately into the antidepressants classification nomenclature and its pharmacological properties also deemed it unfit and inappropriate to be accepted and announced as another separate novel class of antidepressants contrary to the reports published in some previous reference literatures [1–14].

In addition, the two different distinct classes of *N*-methyl-D-aspartate (NMDA) glutamatergic ionoceptor blockers and GABA–A receptor selective positive allosteric modulator antidepressants (GASPAMAs) belonged to the category of rapid-onset antidepressants [1–14].

Future perspective

Future research study to regularly update the classification system of clinically available classes of antidepressants is required. Also, detail future researches will be needed to fully elucidate how the GABAergic, monoaminergic and glutamatergic neurotransmission systems interact together to regulate mood and affective disorders, particularly in depressed patients.

Author contributions

The authors alone are responsible for writing the contents in this research article. We jointly contributed to the study conception and design, writing of introduction, carried out the literature review search, wrote the letter protocol, conducted the research, worked on associated data collection, data analysis, data interpretation, manuscript presentation, writing of discussion, conclusion, recommendations, future perspective, appropriate referencing and approval of the final version of this research article.

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