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Review

Facilitation of Social Support through Negative Allosteric Modulation of α5-Associated $GABA_A$ Receptors: A Novel Mechanism for the Treatment of Depression, Agitation, and Aggression in the Elderly

Jeffrey M. Witkin [1, 2, 3, *], Lalit K. Golani [3], Rok Cerne [2], Md. Toufiqur Rahman [3], Guanguan Li [3], Michael M. Poe [4], James M. Cook [3], Jodi L. Smith [5]

1. Witkin Consulting Group, Carmel, Indiana, USA; E-Mail: witkinconsult@gmail.com
2. Department of Neurological Surgery, Indiana University School of Medicine, Indianapolis, Indiana, USA; E-Mail: rok_cerne@yahoo.com
3. Department of Chemistry & Biochemistry, University of Wisconsin-Milwaukee, Milwaukee, WI, USA; E-Mails: golani@uwm.edu; mdrahman@uwm.edu; guanguan@uwm.edu; capncook@uwm.edu
4. Department of Chemistry, Western Michigan University, Kalamazoo, MI, USA; E-Mail: michael.m.poe@gmail.com
5. Laboratory of Antiepileptic Drug Discovery, Peyton Manning Children's Hospital at St. Vincent; E-Mail: jsmith@goodmancampbell.com

* **Correspondence:** Jeffrey M. Witkin; E-Mail: witkinconsult@gmail.com

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Abstract

Major depressive disorder is a highly-prevalent and debilitating disorder in the aged population. Accumulating clinical evidence suggests a key role for social support in helping to mitigate depression. Preclinical data are reviewed that indicate that selective negative allosteric modulation of α5-containing $GABA_A$ receptors, as with RY-080, might rapidly impact depression in patients. Further, preclinical data in transgenic mice modeling neurodegenerative diseases has suggested that this mechanism might also function to reduce agitation and aggression. These data are discussed in terms of the concept of

Facilitation of Social Support (FOSS). The concept posits that the expression of depression, agitation, and aggression, alone or in concert, reduces social support and thereby weakens this social link as a positive therapeutic intervention. Drugs like RY-080 or other interventions (psychotherapy) that dampen these behaviors will facilitate social support and further help to mitigate these behaviors. Thus, FOSS is proposed as a dual-acting mechanism with one component being drug or therapy-induced suppression of symptoms or disease, and the facilitation of social support that derives from this suppression as component number two. These processes are reciprocal, self-sustaining, and should be additive or synergistic.

Keywords
Depression; social support; $GABA_A$ $\alpha5$; RY-080

1. Introduction

Depression in the elderly, as in the general population is a highly prevalent, costly, and debilitating disorder that is associated with higher than normal morbidity and mortality [1-3]. Prevalence estimates of depression in people 65 years and older have been on the order of 12.5% [4]. Given the general increase in life-expectancy, this problem and its social and economic burden will only increase [5]. Depression in the elderly is highly associated with the risk of suicide [6], cardiovascular disease [7], chronic kidney disease, obstructive pulmonary disease, and Parkinson's disease among other medical conditions [8].

We propose here a theoretical framework that addresses a role for social support in the management of elderly depressed patients. Within this framework, we discuss factors that result in relative social isolation and the value of social support in augmenting ongoing antidepressant approaches (medications and psychotherapy). The conceptual framework is illustrated by example of a medication approach for which preclinical data suggest positive impact on depression, agitation, and aggression in the elderly. It is posited that medications and other interventions that decrease these symptoms and behaviors will facilitate social support (FOSS). It is argued that such medications would act directly and in synergy with social support to provide an augmented wholistic approach to help geriatric patients with these symptoms and behaviors.

Before discussing the FOSS model, rational for the need for additional treatment options are outlined. Standard of care antidepressants are available for the elderly that include the first-line therapies used in the general population. These drugs increase the synaptic availability of biogenic amine neurotransmitters such as 5-hydroxytrytamine (5-HT) or serotonin and norepinephrine (NE) [9]. Conventional antidepressants reduce some symptoms of the disease in only about 1/3 of patients and remission occurs in about1/3 of patients. There remain another third of the population that do not respond to these drugs (treatment-resistant depression) [10]. In elderly depressed patients, the success rate of these drugs is regarded as equal to that of younger patients [11] or relatively low [12]. Further considerations for their use include side-effects and drug-drug interactions that are further threats to elderly patients [12]. Given the issues with conventional antidepressants, other methods of treatment for depression in geriatric patients

have been explored that include psychological therapies of various types including cognitive behavioral therapy [5].

2. Social Isolation and Social Support

One argument for the value of social support for elderly depressed patients comes from the findings that the lack of social support can have a negative impact upon depression. Of the multiple factors that contribute to depression in elderly people, relative social isolation has been shown to be one important factor to consider [11]. Social isolation is associated with depression in elderly and non-elderly patients [13-15] and results in feelings of loneliness and a decline in quality of life [16]. Both social isolation and depression are also significant risk factors for cognitive decline in the elderly [17]. Biological markers associated with depression such as brain-derived neurotrophic factor are also altered by social isolation [18]. Therefore, therapies and practices that address social isolation are in development [19, 20]. Franck and colleagues [21], for example, evaluated a few interventions to reduce social isolation and found that group-based reminiscence therapy was effective in decreasing both social isolation and depression in an elderly population (77-86 years of age). Thus, it has been argued that a reduction in social support can exacerbate and contribute to depression and conversely that facilitation of social support (FOSS) can help to reduce depression and its associated behavioral sequalae [22]. Even the perception of increased social support can be beneficial in depressed patients [23].

Relative social isolation can arise through multiple routes. One reason for social isolation has been suggested to be associated with the behaviors of depressed individuals. Major depressive and anxiety disorders are associated with reductions in adaptive social functioning both during the disease and after remission [24]. Thus, depression and anxiety can themselves increase the likelihood of social isolation that can, in turn, fuel the cycle of isolation and depression. Another set of behaviors that occurs with higher probability in geriatric patients than in the general population includes agitation and aggression [25, 26]. Agitation is associated with depression and cognitive decline [27-29]. Agitated behaviors are highly associated with neurodegenerative disorders such as Alzheimer's disease [15, 30] but also occur in patient's without dementia [31, 32]. Agitated and aggressive behaviors are another inducement for social isolation as they are a serious burden for friends, family, and care-givers [33, 34]. Given the data suggesting that increases in social networks and social support can reduce symptoms of depression and suicidal ideation in the elderly [35], interventions that reduce behaviors of agitation and aggression might help to facilitate social support, mitigate symptoms of depression, and increase the quality of life of these patients.

Unfortunately, the range of effective therapeutic modalities for managing agitation and aggression are severely limited. For acute agitation, standard emergency room procedure generally dictates the use of antipsychotic drugs like haloperidol or benzodiazepine anxiolytics such as diazepam [36]. Although these medications are generally contraindicated in the elderly and in patients with dementias, they are often used in geriatric patients with or without Alzheimer's disease or mixed dementias [37]. It has become increasingly clear that social support might be efficacious in helping to reduce agitation and aggression in elderly patients and as such has been recommended as a first-line treatment option [38].

3. Alpha-5-Containing $GABA_A$ Receptors

We recently reported results of preclinical studies suggesting a biological mechanism that might treat depression and agitation and aggression [39]. We hypothesize that negative allosteric modulation of $GABA_A$ receptors that contain $\alpha5$ protein subunits will reduce depression, agitation, and aggression in patients. Gamma amino-butyric acid (GABA) is the primary inhibitory neurotransmitter in the mammalian central nervous system with $GABA_A$ receptors being the key inhibitory neurotransmitter targets for GABA and exogenous ligands. $GABA_A$ receptors are ligand-gated ion channels comprised of multiple protein subunits [40, 41]. The alpha subunits that make up specific $GABA_A$ receptors determine the pharmacological specificity of compounds and govern the principal pharmacological and biological effects of these compounds on the nervous system and behavior [42]. Post-mortem studies have reported age-related decline in the depression markers BDNF and $GABA_A$ ($\alpha5$) receptors and other associated synaptic proteins [43].

Compounds have been discovered and characterized as selective modulators of $\alpha5$-containing $GABA_A$ receptors [44]. These compounds can function as positive allosteric modulators (PAMs) or negative allosteric modulators (NAMs) of $GABA_A(\alpha5)$ receptors. The selectivity of these compounds for $\alpha5$-containing $GABA_A$ receptors dictates that they have less or no influence on $GABA_A$ receptors associated with other alpha subunits. Compounds modulating $GABA_A$ receptors associated with other alpha subunits can engender somnolence and sedation ($\alpha1$) [45], anxiolytic, antiepileptic, and antinociceptive effects ($\alpha2/3$) [46-48]. The structures of the $\alpha5$-selective $GABA_A$ receptor modulators discussed in the present paper are shown in Figure 1. As an example, the selectivity of the NAM, RY-080, for $\alpha5$ over other α-subtype-containing $GABA_A$ receptors is illustrated in Figure 2.

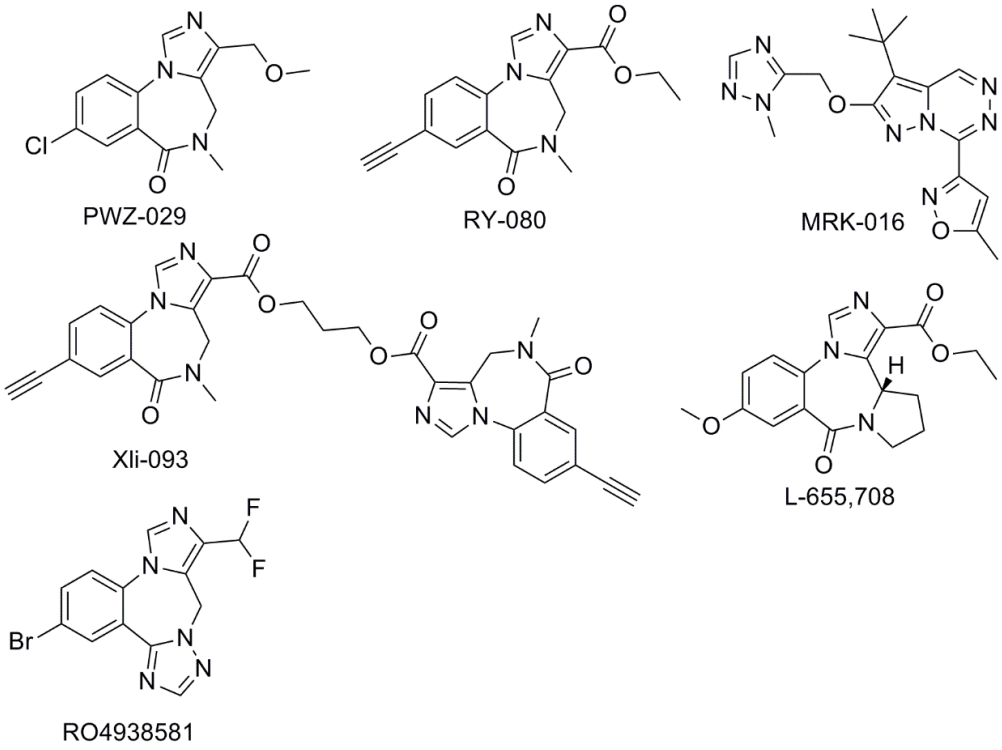


Figure 1 Structures of the $\alpha5$-selective $GABA_A$ receptor ligands discussed.

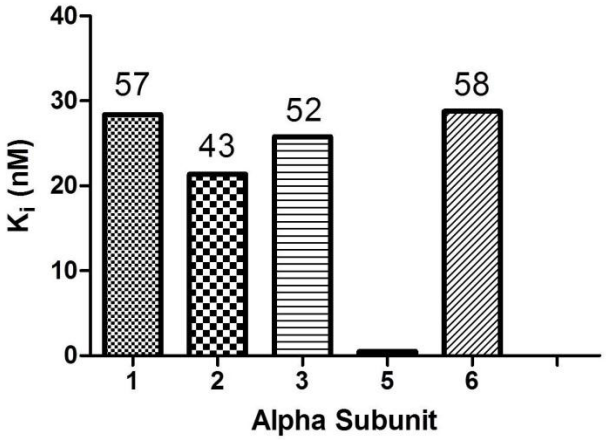


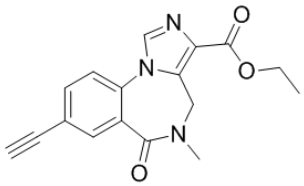
Figure 2 Affinities of the $GABA_A$ receptor NAM, RY-080, for recombinant $GABA_A$ receptors that utilize different alpha protein subunits. Affinities are K_i values in nM. The numbers at the top of the bars represent the fold-selectivity for alpha 5 (0.5 nM). Data are from Liu et al. [49].

Fischell et al. argued that α5-selective NAMs would drive biological responses comparable to ketamine to induce antidepressant responses, but would be devoid of the side-effects that undermine use of ketamine in clinical practice [50]. Ketamine is now well established as a rapid acting antidepressant [51] with (S)-ketamine (esketamine) having just been approved as an antidepressant in 2019. Based upon current understanding that increases in neuronal activity are an initial trigger for ketamine's rapid antidepressant effects, Fischell and colleagues predicted that α5-selective NAMs could initiate the antidepressant biological cascade as well [50]. The receptors are localized within brain areas of relevance (prefrontal cortex and hippocampal pyramidal cells) and α5-selective NAMs had been reported to induce coherent activity in septo-hippocampal circuits that would help regulate mesolimbic pathways involved in mood [52].

L-655,708 and MRK-016 (Figure 1) produced antidepressant-like efficacy in rodent models [50] that are used to predict antidepressant effects in patients. The authors reported that both compounds restored the anti-hedonic effects of stress in the sucrose preference and social interaction tests in rats. In addition, antidepressant-like effects were observed in the forced-swim test [53, 54]. These antidepressant-like effects emerged within 24 hours of a single dose and were long lasting. The antidepressant-like effects of these compounds are postulated to result from their ability to restore the strength of the stress-induced weakening of excitatory synaptic transmission. The levels of AMPA receptor GluA1 were also enhanced [50] with AMPA potentiation being known as a core antidepressant mechanism and one associated with the actions of ketamine [55]. An integral role of α5-containing $GABA_A$ receptors is shown by the fact that L-655,708 can augment induction of NMDA-dependent long-term potentiation and the phosphorylation and synaptic addition of NMDA and AMPA receptors [56]. In turn, AMPA receptor potentiation feeds forward to further enrich synaptic α5-$GABA_A$ receptors [57].

These α5-selective $GABA_A$ receptor NAMs also produced antidepressant-like effects in the forced-swim assay [53, 54], another model predictive of human antidepressant efficacy. The antidepressant-like effects of L-655,708 were evidenced after a single injection and were long-lasting [53].

Although these NAMs produced antidepressant-like effects, their mechanism of action had yet to be definitely assigned. In addition to the selectivity of these molecules for $GABA_A$ ($\alpha5$) receptors over other alpha subunit configurations, two additional pieces of data were recently brought to bear on this question. First, the antidepressant-like effects were related to the negative intrinsic efficacy of the compounds. Xli-093 (Figure 1), an antagonist, was not active in the forced-swim assay. PWZ-029 (Figure 1), a partial NAM, was modestly active, and the stronger NAM, RY-080 (Figure 1), was fully efficacious in producing effects comparable to the tricyclic antidepressant imipramine [39]. Secondly, the antidepressant effects of RY-080 were blocked both by Xli-093 and by PWZ-029 as predicted by receptor theory [39] (Figure 3).



RY-080

Effect	**Model**	**Controls**
Antidepressant	Mouse forced-swim assay	Comparable effect to imipramine
Anti - Agitation	rTg4510 mouse	No effect in wild-type mice
Anti - Aggression	rTg4510 mouse	No effect in wild-type mice

Mechanism of Action

Antidepressant effect of $GABA_A$ ($\alpha5$)-selective NAM, RY-080, blocked by:
Xli-093 – $GABA_A$ ($\alpha5$)-selective antagonist
PWZ-029 – $GABA_A$ ($\alpha5$)-selective partial agonist

Figure 3 Summary of effects of the $\alpha5$-selective $GABA_A$ receptor NAM, RY-080, in mouse models and its mechanism of action. Data are from Xu et al [39].

rTg4510 mice are a transgenic mouse line designed to accumulate pathological tau which is a putative contributor to neurodegenerative diseases like Alzheimer's disease [58]. These mice develop an age-dependent, tau-associated explosive hyperactivity [59, 60] that might be relevant to modeling agitation and aggression in neurodegenerative disease states as postulated by Xu et al. [39]. In addition to its antidepressant-like efficacy, RY-080 also selectively attenuated the agitated hyperactivity of aged rTg4510 mice (Figure 3). That is, RY-080 reduced the agitated hyperactivity of rTg4510 mice but did not reduce the hyperactivity observed in non-pathological or wild-type mice [39] (Figure 3). These data in the transgenic mice suggest the potential for NAMs of $GABA_A$($\alpha5$) receptors to help attenuate the amotivational, agitated and aggressive states that arise in neurodegenerative disorders where depression is a primary comorbid symptom. Another NAM selective for $\alpha5$-comprised $GABA_A$ receptors, RO4938581 (Figure 1), suppressed the hyperactivity in another transgenic mouse line, Ts65Dn mice, in the open field and plus maze [61]. However, as the basis for the connection of this mechanism to agitation and aggression is based primarily on

these transgenic mouse data, additional data will be needed to test the idea that negative allosteric modulation of α5-comprised $GABA_A$ receptors might be a viable treatment option for these behavioral symptoms.

Ketamine produces a host of undesirable side-effects including motor impairment, hyperexcitability, psychotomimetic effects, abuse liability, and brain lesions after chronic abuse [30, 62-64]. In contrast, the α5-selective $GABA_A$ receptor mechanism does not engender ketamine-associated side effects or produce effects predictive of abuse liability [39, 53, 54]. One compound, MRK-016 (Figure 1), has been studied in humans. It is tolerated and does not produce anxiogenic, epileptogenic, or hallucinogenic effects [65]. MRK-016 therefore is a potential compound for clinical investigation in depressed patients although it was not well-tolerated in elderly patients [66].

Negative allosteric modulation of $GABA_A$ (α5) receptors has also been predicted from preclinical data to be cognitively enhancing. As such, α5-containing $GABA_A$ receptors have also been considered as potential drug targets for augmentation of cognition and therapeutic impact in Down's syndrome and other disease states [44, 67]. Given the cognitive decline that can arise in geriatric patients [68], the comorbidity of cognitive impairment and depression [69], and the lingering cognitive clouding even after mood remission [70], the ability to positively augment cognitive function is likely to be value added. Selective α5 $GABA_A$ receptor NAMs have been reported to produce cognitive augmentation under a host of deficit conditions [42]. As such, selective NAMs for these receptors have been developed as cognitive enhancers [65, 71-73].

In addition to NAMs, antagonists at α5-containing $GABA_A$ receptors have also been shown to produce enhancements in cognitive functioning [44, 74]. For example, an antagonist, S44819, has recently been shown to be active in rodent models of vascular cognitive impairment [75], a disorder of high prevalence in the geriatric community [76]. S44819 has been studied in healthy humans where it was shown to increase cortical excitability [77]. It has also just been reported that a series of compounds that are positive allosteric modulators (PAMs) of α5-containing $GABA_A$ receptors were also antidepressant and protected against stress [78]. $GABA_A$ (α5) receptor PAMs have also shown efficacy against age-induced cognitive decline [78, 79]. Although the mechanisms associated with PAMs or NAMs of α5-containing $GABA_A$ receptors needs to be further explored, the data from Prevot et al. point to another inroad into helping the elderly with depression, anxiety, and cognitive impairments [78].

The $GABA_A$ (α5) receptor hypothesis states that NAMs of $GABA_A$ (α5) receptors will be antidepressant, decrease agitation, and dampen aggression. However, the $GABA_A$ (α5) receptor hypothesis is based upon animal model data. Therefore, clinical evaluation of compounds will be required to ascertain the veracity of the claims fostered by the preclinical literature. Although some clinical evaluation of this mechanism has begun, there has been no success to date in moving these molecules into full development. For example, the NAM, α5IA reduced ethanol-induced amnesia in healthy volunteers [80]. However, renal toxicology in preclinical studies prevented further development of this compound. MRK-016 was poorly tolerated in elderly patients [66]. Development of PET ligands for $GABA_A$ (α5) receptors appears to be ongoing [81].

4. A Facilitation of Social Support Model

Clinical observations for depression, agitation, aggression, and their relationship to social isolation and social support (discussed earlier) suggest a dynamic system whereby social support can play a key role in the quality of life of elderly patients suffering from depression [22]. The more general concept of facilitation of social support (FOSS) as a driver of therapeutic benefit is illustrated in Figure 4**.** Here, depression, agitation, and aggression, separately and in concert, negatively impact social support. In turn, this reduction in social support exacerbates these symptoms and behaviors. The interactions shown in this Figure show how FOSS can help alleviate mood and agitation and aggression. Reducing symptoms of depression, agitation, and/or aggression by RY-080 or by other means (as discussed above) would add a brake to the negative influence of these symptoms on social support. In turn, the ensuing enhancement of social support would positively feedback to mitigate symptoms of depression, agitation, and aggression. This system thus provides a dual mechanistic approach to positively influence depression in the elderly, first by directly impacting major depressive disorder. Secondarily, the direct suppression or attenuation of depression symptoms, agitation, and/or aggression would further drive therapeutic benefit by enhancing the social support networks that nurture depressed patients and work to calm the agitated and aggressive states that conspire to undermine it. Thus, α5-selective NAMs are hypothesized to directly decrease depression, agitation, and aggression. But, in addition, symptom demise or decline is predicted to bring into play another mechanism – social support, previously hurt by their presence.

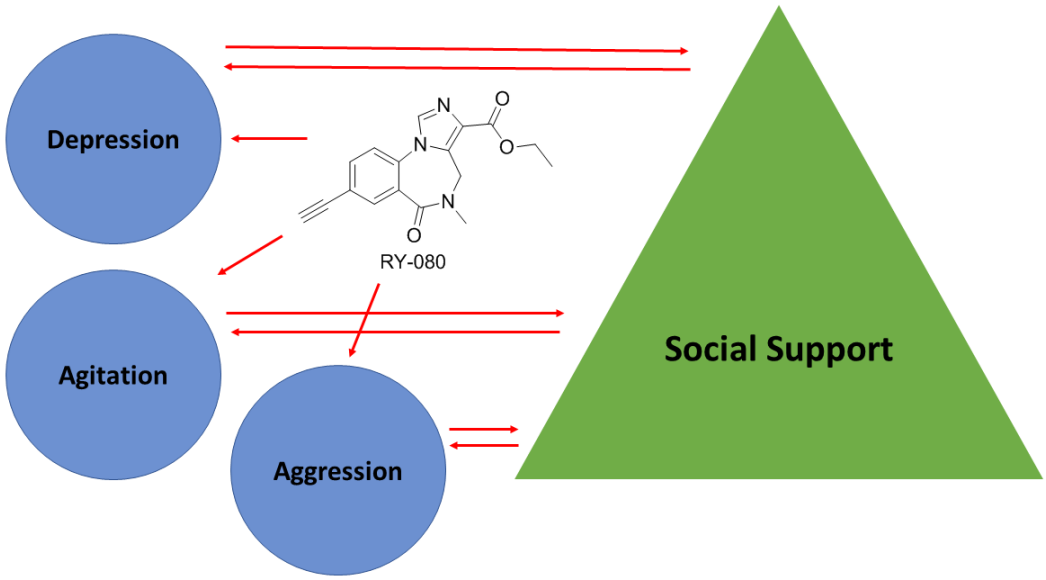


Figure 4 A model describing the concept of facilitation of social support or FOSS as one part of a therapeutic program to help attenuate major depressive disorder, agitation, and/or aggression in elderly patients. The model also shows the second part of the therapeutic intervention as one that directly impacts mood, agitation, and/or aggression. Other drugs or therapies could be substituted for the α5-selective $GABA_A$ receptor negative allosteric modulator RY-080.

The FOSS hypothesis is testable. Therapeutic intervention by drugs or other means (e.g., psychotherapy) of any one component should reciprocally impact social support and the component modified. Changes in outputs could be made in both directions through natural experiment. The idea of whether these factors work in isolation, by additivity, or synergistically could also be tested. Finally, one could control the degree of social support feedback in experimental settings – For example, if agitation is decreased but social support is artificially restricted, is the impact to the intervention on agitation less than if social support were naturally facilitated by a reduction in agitation?

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Conflict of Interest: The authors declare no conflicts of interest. All data reported in the present review are from the public scientific literature.

Author Contributions

Conceived FOSS model: JMW; wrote and edited manuscript: all authors; provided needed materials: LKG, MTR, GL, MMP, JMC.

Competing Interests

The University of Wisconsin-Milwaukee holds patents for some of the alpha 5 compounds discussed including Xli-093, PWZ-029, and RY-080.

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