Published in final edited form as:

Biol Psychiatry. 2018 June 01; 83(11): 955–962. doi:10.1016/j.biopsych.2018.03.001.

Metabotropic glutamate receptor 5 as a target for the treatment of depression and smoking: robust preclinical data but inconclusive clinical efficacy

Samuel A. Barnes¹, Douglas J. Sheffler², Svetlana Semenova^{1,5}, Nicholas D. P. Cosford², and Anton Bespalov^{3,4}

¹Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0603, La Jolla, CA 92093, USA

²NCI-Designated Cancer Center, Sanford Burnham Prebys Medical Discovery Institute, 10901 North Torrey Pines Road, La Jolla, CA, 92037, USA

³EXCIVA, Am Aukopf 14/1, Heidelberg 69118, Germany

⁴Valdman Institute of Pharmacology, Pavlov Medical University, 6/8 Lev Tolstoy Str., St. Petersburg 197022, Russia

⁵PAREXEL International, 1560 E Chevy Chase Dr, suite 140, Glendale, CA 91206, USA

Abstract

The ability of novel pharmacological compounds to improve outcomes in preclinical models is often not translated into clinical efficacy. Psychiatric disorders do not have biological boundaries and identifying mechanisms to improve the translational bottleneck between preclinical and clinical research domains is an important and challenging task. Glutamate transmission is disrupted in several neuropsychiatric disorders. Metabotropic glutamate (mGlu) receptors represent a diverse class of receptors that contribute to excitatory neurotransmission. Given the wide, yet region-specific manner of expression, developing pharmacological compounds to modulate mGlu receptor activity provides an opportunity to subtly and selectively modulate excitatory neurotransmission. This review focuses on the potential involvement of mGlu5 receptor disruption in major depressive disorders (MDD) and substance use disorders (SUD). We have provided an overview of the justification of targeting mGlu5 receptors in the treatment of these disorders, summarized the preclinical evidence for negatively modulating mGlu5 receptors as a therapeutic target for MDD and nicotine dependence and highlighted the outcomes of recent clinical trials. While the evidence of mGlu5 negative allosteric modulation has been promising in preclinical investigations, these beneficial effects have not translated into clinical efficacy. In this review, we have identified key challenges that may contribute to poor clinical translation and

Correspondence should be addressed to Dr. Samuel A. Barnes, Ph.D. (sabarnes@ucsd.edu) or Dr. Anton Bespalov, MD Ph.D. (anton.bespalov@exciva.com).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

SAB, DJS, SS, NDPC, and AB report no biomedical financial interests or potential conflicts of interest.

provided suggested approaches moving forward to potentially improve the translation from preclinical to clinical domains. Such approaches may increase the success of clinical trials, and may reduce the translational bottleneck that exists in drug discovery for psychiatric disorders.

Keywords

mGlu5 receptor; major depressive disorder; substance use disorder; negative allosteric modulator; drug discovery; cross-species translation

A significant body of evidence indicates that metabotropic glutamate receptor subtype 5 (mGlu5) negative allosteric modulators (NAMs) have the potential to treat a number of central nervous system (CNS) disease states. Consequently, there have been multiple drug discovery programs aimed at delivering potent and selective mGlu5 NAMs for the treatment of patients with depression or substance/alcohol use disorders. Yet, despite decades of research, robust data in preclinical models of therapeutic efficacy, and several selective mGlu5 NAMs advanced into human studies, it remains unclear whether these compounds may be of any therapeutic value in humans suffering from depression and/or substance/alcohol use disorders.

The limited translation of promising preclinical data into clinical efficacy is a challenge for all therapeutic areas, including psychiatry. There are several excellent reviews dedicated to the analysis of the underlying causes for this limited translation (1, 2). Here we review the preclinical and clinical outcomes of mGlu5 NAMs in the treatment of MDD and SUD, and analyze factors that could affect translatability of preclinical efficacy for this drug class. We dedicate our work to the memory of our late colleague, mentor, and friend, Professor Athina Markou, who was passionate about identifying therapies for these therapeutic indications and whose work is foundational to our current understanding of the role of mGlu5 in psychiatric pathology.

1. mGlu5 as a drug target

Glutamate exerts excitatory neurotransmission through ionotropic or metabotropic glutamate receptors (mGlu). Ionotropic glutamate receptors (consisting of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), or kainate receptors) facilitate fast neurotransmission through these glutamate-gated ion channels. In contrast to the ionotropic glutamate receptors, mGlu are G protein-coupled receptors. There are three groups of mGlu that are categorized by their distinct structure, sequence homology, synapse location, pharmacological selectivity and impact on cellular physiology (3, 4): Group I mGlu are comprised of mGlu1 and mGlu5, group II - mGlu2 and mGlu3, and group III - mGlu4, mGlu6, mGlu7, and mGlu8. Given the wide, yet region-specific, expression of different mGlu throughout the brain, targeting mGlu receptors offers a unique advantage to modulate glutamate transmission in a comparatively subtle and specific manner (5). There are a number of excellent review papers that summarize the current knowledge of mGlu5 biology and its physiological impact (3, 6, 7). For the purposes of this review, we highlight four aspects that make mGlu5 particularly attractive as a therapeutic target.

First, mGlu5 has proven to be amenable to therapeutic intervention with small molecule compounds (drugs). While antagonists at the glutamate recognition site (competitive antagonists) are typically of low-potency and lack selectivity against other mGlu subtypes, several highly potent and selective NAMs that act as non-competitive antagonists with excellent CNS penetration and *in vivo* efficacy have been discovered (8, 9). Several mGlu5 NAMs have been advanced into clinical development to evaluate their efficacy and safety in patients with either Parkinson's disease or Fragile × syndrome (10, 11).

Second, translational programs involving mGlu5 NAMs can be supported by target engagement information generated using positron emission tomography (PET) ligands in both humans and animals (12–15). In humans, one such radiotracer, [¹¹C]ABP688, showed high binding in mGlu5-rich regions including the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), medial temporal lobe, striatum and amygdala (16). Structural and/or functional alterations in these structures are often seen in MDD and substance abuse (17, 18). Thus, PET imaging, using mGlu5 tracers, allows investigators to determine target engagement of novel compounds, either during clinical trials or preclinical exploratory investigations, targeting mGlu5-rich brain regions that are implicated in both MDD and substance abuse. As disruptions in glutamate transmission are evident in these patient populations (19, 20), negatively modulating mGlu5 activity in brain structures implicated in disease pathophysiology may be an attractive strategy to mediate some of the symptoms associated with these disorders. Importantly, PET imaging data can guide dose selection for clinical trials and translate doses that are effective in preclinical investigations.

Third, group I mGlu5 positively modulate the effects of glutamate acting on NMDA receptors (21, 22). Antagonism of mGlu5 decreases glutamate neurotransmission by, at least in part, diminishing the activity of ionotropic NMDA receptors (23). This phenomenon results from multiple scaffolding proteins (e.g., Homer, Shank, PSD-95) that physically and functionally link mGlu5 to NMDA receptors (24). It is well known that the NMDA receptor antagonist, ketamine, produces immediate relief in patients with treatment-resistant depression (25). This robust effect generated a major interest to identify drugs with ketamine-like efficacy but devoid of its adverse effects. Importantly, it has recently been shown that the antidepressant response of acute ketamine exposure in humans was associated with a reduction in mGlu5 availability (26). Since mGlu5 NAMs downregulate NMDA receptor activity (6), mGlu5 antagonism may produce a similar therapeutic response as an NMDA receptor antagonist.

Fourth, antagonism of mGlu5 and the resulting reduction in glutamate transmission may have therapeutic potential in some disease states associated with increased glutamate transmission, such as drug abuse (27) and MDD (19, 28). Interestingly, [¹¹C]ABP688 binding was decreased in several cortical regions, including the OFC, ACC and hippocampus, in patients with MDD (29), and in the medial OFC of smokers (30). The reduction in [¹¹C]ABP688 binding was also evident in recent ex-smokers, but, interestingly, absent in long-term ex-smokers (31). Collectively, these findings suggest that reduced mGlu5 binding seen in smokers or MDD may represent either a risk factor that increased the likelihood of smoking, or was a compensatory adaptation to the chronic elevations in glutamate levels evident in smokers (32) or MDD^{24,25}. These commonalities further support

the notion that these distinct conditions potentially share overlapping mechanisms that may be jointly exploited.

Altogether, the existing evidence briefly summarized above indicates that mGlu5 is an excellent target to validate preclinical concepts such as the role of glutamate in depression and SUD.

2. Evidence supporting the therapeutic use of mGlu5 NAMs

2.1 Depression: Scientific rationale and preclinical evidence

mGlu5 antagonists have been studied using several preclinical methods commonly used in antidepressant drug research. In behavioral despair tests such as the forced swim and tail suspension, administration of both mGlu5 NAMs (33, 34) and genetic deletion of mGlu5 decreased immobility suggesting an anti-depressant like activity (35, 36). While most supporting evidence has been generated using acute stress models (stress-induced hyperthermia, elevated plus maze, Vogel test, conditioned emotional response, novelty-suppressed feeding, fear-potentiated startle, forced swim, tail suspension, etc.), efficacy of several mGlu5 NAMs have also been confirmed using more sophisticated methods – olfactory bulbectomy (37), chronic social defeat (38), and chronic mild stress (39). For example, repeated administration of basimglurant (mGlu5 NAM) reduced anhedonia in rats exposed to chronic mild stress (40). In most, if not all, studies that used behavioral readouts to assess efficacy of mGlu5 NAMs, their efficacy was comparable to that of currently used monoaminergic antidepressants (such as serotonin-selective reuptake inhibitors). Further, studies using non-behavioral methods have revealed effects of mGlu5 NAMs such as basimglurant that are shared by conventional antidepressant drugs (e.g., suppression of REM sleep in the absence of any appreciable effects on non-REM sleep) (40). Even fMRI-based quantitative comparison of the brain activity patterns suggested strong similarities between basimglurant and prototypical antidepressants (40).

However, one should note that the true predictive validity of these methods (as opposed to “retrospectively” established predictive validity) (1, 41) is not established. Therefore, given the robustness of ketamine’s antidepressant action in humans (42), the above mentioned ability of mGlu5 antagonists to mimic effects of NMDA receptor antagonists at various levels of analysis (from cellular to systemic) is amongst the main arguments supporting predictions of potential antidepressant efficacy of mGlu5 NAMs.

The rapid and sustained antidepressant response of ketamine exposure has been suggested to result from synaptogenesis induced by the activation of mTOR signaling pathways (43) (see, however, reports challenge the robustness of these findings (44)) or activation of AMPA receptors (45). Although mGlu5 signaling does influence mTOR signaling (46), mTOR activation does not seem to be involved in the rapid antidepressant effects induced by the mGlu5 NAM MTEP (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine) or its close structural analogue MPEP (2-methyl-6-(phenylethynyl)pyridine) (47, 48). Further, while mGlu5 activation can lead to an internalization of AMPA receptors (49), the antidepressant action of mGlu5 antagonism does not seem to be prevented by AMPA receptor antagonists (50, 51), in contrast to what was reported for ketamine (52).

In summary, most available preclinical evidence suggests antidepressant-like profile of mGlu5 NAMs. As described below, these promising preclinical findings have not translated to convincing clinical efficacy.

2.2 Depression: Clinical data

There have been several clinical trials completed to-date that have evaluated the utility of mGlu5 NAMs in patients with depression. Basimglurant (RG-7090; RO-4917523) was first studied in a randomized, double-blind, placebo-controlled, Phase II trial (NCT00809562) in patients with treatment-resistant depression. Results were not reported but, soon after that exploratory study was completed, a larger Phase II trial (NCT01437657) was initiated in patients with an inadequate response to antidepressant therapy who received placebo or one of the two doses of basimglurant (0.5 mg or 1.5 mg) for 6 weeks (53). In this trial, there was a non-significant trend towards improvement in the clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS), which was the pre-specified primary endpoint. However, antidepressant efficacy in some secondary and exploratory endpoints 16-item Quick Inventory of Depressive Symptomatology–Self Report and patient-rated MADRS) was evident in the 1.5 mg basimglurant treated patients. Further, it was acknowledged that this trial did not include an active comparator and a high placebo effect could have an impact, common for antidepressant drug trials. According to the results of the PET study conducted in healthy volunteers (NCT01483469), mean steady-state concentrations of basimglurant after 14 days of once daily oral treatment (i.e., as in the clinical efficacy trials) result in receptor occupancy of approximately 25% at 0.5 mg and 53% at 1.5 mg.

In addition to these studies on basimglurant, a second mGlu5 NAM, AZD2066, has also been studied in the Phase II clinical trials in patients with MDD (see results at the clinicaltrials.gov website; NCT01145755). In this trial, neither AZD2066, nor duloxetine, an active comparator, had separated from placebo. While the placebo response is a commonly recognized problem in clinical research, it should be noted that at the doses used in this trial (12 and 18 mg) AZD2066 may only reach 50% mGlu5 receptor occupancy at the C_{max} (54).

In summary, the current clinical data on mGlu5 NAMs as putative antidepressants is inconclusive. First, known attempts to deliver clinical proof-of-concept (POC) have been met with challenges such as the placebo effect, which makes it difficult to reveal efficacy even for drugs with an established role in therapy for patients with MDD. Second, both basimglurant and AZD2066 have been studied up to exposures that are associated with about 50% receptor occupancy. It is yet to be established whether receptor occupancy levels significantly higher than 50% are necessary to observe clinical efficacy.

2.3 Nicotine addiction: Scientific rationale and preclinical evidence

The addictive properties of nicotine are hypothesized to result from the effect nicotine has on mesocorticolimbic dopamine transmission (55). In the CNS, nicotine activates excitatory nicotinic acetylcholine receptors (nAChRs), some of which are expressed on dopamine neurons in the ventral tegmental area (VTA) (4). Activation of these receptors increases elevates dopamine concentrations in target structures (55), contributing to the development of drug dependence (56, 57). In addition, glutamate transmission is also modulated by

nicotine (58). nAChRs are expressed on pre-synaptic glutamate neurons (32). Nicotine exposure would activate nAChRs on these glutamate terminals, increase cellular excitability and release glutamate within the VTA, which in turn would activate ionotropic or metabotropic glutamate receptors located on VTA dopamine neurons (4, 5, 58, 59). Thus, changes in glutamate transmission through mGlu5 may play a critical role in nicotine dependence by further contributing to changes in dopamine transmission.

In support of the above described mechanistic evidence, Dr. Markou's group determined that mGlu5 activity may be involved in the reinforcing aspect of nicotine consumption. For example, administration of the mGlu5 NAM MPEP diminished the nicotine-induced elevation of dopamine transmission in the nucleus accumbens (60), providing a neurochemical mechanism explaining why mGlu5 antagonism reduced nicotine-induced conditioned place preference (61), the breakpoint for nicotine administration (62), nicotine self-administration (63), and cue- and schedule-induced reinstatement of extinguished nicotine self-administration (64) in rodents. Importantly, Dr. Markou's group, and others, demonstrated that the mGlu5 NAM-induced reduction in drug self-administration did not reflect a generalized reduction in motivation (65, 66).

The seminal work led by Dr. Athina Markou identified that nicotine withdrawal impairs brain reward function in rodents, as reflected by lower thresholds of intracranial self-stimulation (ICSS) (67). This disruption in reward function is not only similar to that observed following withdrawal from other drugs of abuse, but is also reminiscent of the negative affective state that smokers experience during early nicotine cessation. An anhedonic state, characterized by elevated ICSS thresholds, emerged also after repeated exposure to stress, such as chronic social defeat (68, 69) that involved repeatedly exposing a subordinate rodent to a dominant rodent (70). Given the suspected role of glutamate neurotransmission in the negative affective state that emerged during acute nicotine withdrawal (5) and the hypothesized antidepressant properties of mGlu5 NAMs, these agents may be well suited for reversing the nicotine withdrawal-induced deficits in brain reward function. However, experimental evidence does not support these predictions. An mGlu5 NAM was found to worsen symptoms of nicotine withdrawal in rats (71). However, as nicotine reinstatement was reduced (64), an mGlu5 NAM may be more effective once acute withdrawal has subsided.

In summary, while mGlu5 antagonism may be useful in reducing tobacco smoking, administration of mGlu5 NAMs during early abstinence may worsen the negative affective state associated with nicotine withdrawal.

2.4 Nicotine addiction: Clinical evidence

Mavoglurant (AFQ-056) is the only mGlu5 NAM that has been tested clinically as a potential treatment to facilitate smoking cessation. In this double-blind placebo-controlled POC study (NCT00414752), smokers received mavoglurant, nicotine (as active comparator) or placebo, with the primary outcome measure of reduction of craving by self-report questionnaires during 3 days of voluntary smoking stoppage. The trial was completed in June 2007 but the results have not been disclosed. Importantly, it should be noted that this study utilized an mGlu5-based strategy to ameliorate craving during early, voluntary

abstinence. As discussed above, mGlu5 antagonism during acute nicotine withdrawal exacerbated impairments in brain-reward function (71). Decreasing the severity of the negative affective state experienced during nicotine withdrawal would increase the chances of maintaining abstinence. Mavoglurant treatment may, therefore, have had greater chances for success if the trial was designed with this information taken into account.

3. Challenges in predicting clinical efficacy of mGlu5 NAMs

3.1. Treatment duration

The vast majority of preclinical efficacy studies using novel psychopharmacological agents are conducted using acute treatment schedules. This practice is in sharp contrast to the common pattern of clinical use of pharmacotherapeutics. Given the unique plasticity of brain mechanisms, effects of many drugs may change over time, and thereby limit apparent translatability of preclinical efficacy claims. Further, there are several cases of opposite or different effects observed in animals treated with mGlu5 NAMs *vs.* genetically modified animals with altered mGlu5 function. One example comes from the studies on stress-induced behaviors where mGlu5 NAMs produced anti-depressant-like effects in rats (47) while mGlu5 knockout (KO) increased stress-induced social deficits and learned helplessness (36). Interestingly, the depressive-like phenotype was reversed when mGlu5 expression was restored in the nucleus accumbens of mGlu5 KO mice (36). Moreover, mice lacking mGlu5 throughout the brain (global mGlu5 KO mice) did not show nicotine-withdrawal induced anhedonia or evidence of withdrawal-induced somatic signs (72), whereas mGlu5 NAM MPEP worsened these symptoms in rats (71).

There are many factors that could explain different effects of acute administration of mGlu5 NAM and mGlu5 KO – animal species (studies on mGlu5 NAMs in rats *vs.* receptor KO in mice), development aspects of mGlu5 KO, different degree of receptor function suppression (100% in case of receptor KO *vs.* presumably significantly lower receptor occupancy in the NAM experiments, etc). These factors can be directly analyzed using readily available research tools and methods. Such efforts, together with additional studies on repeated administration of mGlu5 NAMs in preclinical efficacy models should be sufficient to answer a question as to whether there is any disconnect between acute drug treatment in animals and weeks- or months-long therapy in humans.

3.2. Target engagement

Clinical efficacy can be diminished if the molecule did not appropriately engage the biological mechanism targeted by the hypothesis. Despite progress in the ability of clinical pharmacokinetics to predict dose/exposure relationships of new drugs, establishing clinically efficacious exposures from preclinical experiments remains challenging, in part due to the complexity of the brain including the blood brain barrier. There are various modeling tools (73) used to assist with these assessments, but direct target recognition assays, such as the use of PET imaging (13) to demonstrate target occupancy in animals and humans are becoming more widespread. As discussed above, several PET tracers for mGlu5 have been developed and successfully applied to estimate receptor occupancy for mGlu5 NAMs that were advanced into human POC studies. Unfortunately, for the compounds discussed above

(basimglurant, AZD2066, mavoglurant), data comparing receptor occupancy in both humans and animals are lacking.

In addition, there were several adverse effects observed in humans exposed to mGlu5 NAMs including cognitive deficits, adverse skin reactions, dizziness and visual hallucinations (74–76). Although these effects are likely to be mechanism-related, this information does not help to establish whether doses used in humans reached receptor occupancy levels that are associated with efficacy in preclinical studies. Similar adverse events have also been reported in preclinical investigations (77). However, it should be noted that mGlu5 NAMs have been advanced into clinical development for disorders such as Parkinson's disease and Fragile $\times$ syndrome (10, 11). Further studies to optimize the dose required for clinical efficacy, while reducing the on-site adverse effects may assist with this unwanted feature of mGlu5-based therapeutics.

Thus, there are plenty of tools and approaches to confirm that the human POC studies were conducted using the drug doses that produce target occupancy that the preclinical investigations establish as the required for efficacy. This analysis can currently not be completed due to significant gaps in the publicly available information on preclinical and clinical efficacy profile of mGlu5 NAMs. Addressing this missing link between preclinical and clinical datasets may be an important step in improving the translatability between research domains.

3.3. Physiological processes vs. pathology states

Glutamate is the major excitatory neurotransmitter and mGlu5 is expected to play a role in various physiological processes that can be altered in pathology in a region- and/or neuron-specific manner. For example, deletion of mGlu5 on glutamatergic neurons induced depressive-like phenotypes, whereas deletion of mGlu5 from GABAergic neurons produced anti-depressive-like behaviors (78). Thus, the pharmacodynamic profile of an mGlu5 NAM can be significantly affected by whether the drug is tested in presumably normal or diseased subjects. In addition, expression of mGlu5 is subject to circadian variation (79), an effect that was more pronounced in females (80). Hence, the time of mGlu5 NAM administration and sex in both preclinical and clinical studies must be taken into account (13).

Psychiatric diseases, as defined by the diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD), do not have biological boundaries that support the development of novel medications. This problem is well recognized, and efforts, such as the National Institute of Mental Health's Research Domains Criteria (RDoC) program (81), have been launched. Such an approach is based on the identification of pathological states that are currently not among recognized therapeutic indications (from a regulatory perspective) but are mechanistically well understood, can be readily studied in laboratory animals, and where preclinical efficacy of novel drugs is more likely to be confirmed in humans.

Until RDoC delivers specific tools and methods, one may need to give extra value to clinical characteristics of the disease that can be built into currently existing animal models. For example, anhedonia, characterized by reduced reward responsiveness, can be measured in

both humans and animals, and is blunted in both humans with MDD (82) and undergoing nicotine withdrawal (83) as well as rodents subjected to chronic social stress (68) or nicotine withdrawal (83, 84) (see review by Der-Avakian and Pizzagalli, Current Issue). Hence, using novel pharmacological compounds with preclinical tests with a high degree of cross-species translational validity to modulate clinical characteristics observed in humans may better identify compounds that display clinical efficacy. Alternatively, identifying biologically defined subpopulations may be important. For example, there are MDD patients who demonstrate abnormal responses to dexamethasone (85) – i.e. lack of or reduced suppression of HPA axis activity. This phenomenon has also been observed in some animal models such as learned helplessness (LH) (86). Interestingly, a 21-day long treatment of the LH rats with an mGlu5 NAM MPEP did not reverse LH (87), suggesting that perhaps models like LH can be used to identify markers to identify patient population that is more or less likely to respond to such pharmacotherapeutic intervention.

4. Path forward

The influential work led by Dr. Markou over the last 20 years, beginning with the demonstration that nicotine withdrawal induced dramatic decreases in brain reward function (67), identified the involvement of mGlu5 functionality, and the modulation of behaviors central to MDD and drug abuse.

Despite the wealth of preclinical evidence suggesting antidepressant-like effects of mGlu5 NAMs, mechanistic proximity to ketamine and encouraging clinical data on basimglurant, there is a lot of uncertainty regarding therapeutic utility of mGlu5 NAMs as antidepressants. Although mGlu5 remains a target of interest for various psychiatric disorders including MDD and continues to be further explored (NCT02727972), there are currently no ongoing clinical trials on mGlu5 NAMs in depression. This lack of ongoing mGlu5 NAM MDD trials is most likely explained by pharmaceutical companies becoming much less interested in depression as a therapeutic indication given a high rate of failures in preclinical-to-clinical translation of efficacy claims. While there are many factors that contribute to these failures (e.g., strong placebo effects in clinical trials), it has to be emphasized that the case of mGlu5 NAMs is far from being closed.

The biggest challenge to understanding gaps in preclinical-to-clinical translation for this drug class is the limited access to information that was generated by drug companies in preclinical labs and clinical trials. Closing the knowledge gaps between preclinical and clinical research, by including chronic treatment regimens in animals, understanding receptor occupancy in both animal and human subjects, carefully considering the time of drug treatment, using tasks with high cross-species translational validity, and/or identifying pharmacodynamics in previously untested (sub)populations of animals (i.e., including female subjects) is essential if the field of psychiatry research is to break the translational bottleneck that is currently being experienced. Taking this path is essential to prepare an adequate translational strategy for developing mGlu5 NAMs for therapeutic use in humans, eventually improving the quality of life for patients with MDD and/or SUD.

Acknowledgments

This work was funded in part by National Institute of Mental Health grant funding (R01MH108653 and R01MH106865), a National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award, and a NARSAD Dylan Tauber Young Investigator Award.

References

1. Markou A, Chiamulera C, Geyer MA, Tricklebank M, Steckler T. Removing Obstacles in Neuroscience Drug Discovery: The Future Path for Animal Models. *Neuropsychopharmacology*. 2009; 34:74–89. [PubMed: 18830240]
2. Young J, Geyer M. Developing treatments for cognitive deficits in schizophrenia: The challenge of translation. *Journal of psychopharmacology*. 2014; 29(9):178–196. [PubMed: 25516372]
3. Niswender CM, Conn PJ. Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu Rev Pharmacol Toxicol*. 2010; 50:295–322. [PubMed: 20055706]
4. Kenny PJ, Markou A. The ups and downs of addiction: role of metabotropic glutamate receptors. *Trends Pharmacol Sci*. 2004; 25:265–272. [PubMed: 15120493]
5. Markou A. Metabotropic Glutamate Receptor Antagonists: Novel Therapeutics for Nicotine Dependence and Depression? *Biol Psychiatry*. 2007; 61:17–22. [PubMed: 16876138]
6. Newell KA, Matosin N. Rethinking metabotropic glutamate receptor 5 pathological findings in psychiatric disorders: implications for the future of novel therapeutics. *BMC Psychiatry*. 2014; 14:23. [PubMed: 24472577]
7. Homayoun H, Moghaddam B. Group 5 metabotropic glutamate receptors: role in modulating cortical activity and relevance to cognition. *Eur J Pharmacol*. 2010; 639:33–39. [PubMed: 20371231]
8. Lindsley CW, Emmitte KA. Recent progress in the discovery and development of negative allosteric modulators of mGluR5. *Current opinion in drug discovery & development*. 2009; 12:446–457. [PubMed: 19562641]
9. Rodriguez AL, Grier MD, Jones CK, Herman EJ, Kane AS, Smith RL, et al. Discovery of Novel Allosteric Modulators of Metabotropic Glutamate Receptor Subtype 5 Reveals Chemical and Functional Diversity and In Vivo Activity in Rat Behavioral Models of Anxiolytic and Antipsychotic Activity. *Molecular pharmacology*. 2010; 78:1105–1123. [PubMed: 20923853]
10. Petrov D, Pedros I, de Lemos ML, Pallas M, Canudas AM, Lazarowski A, et al. Mavoglurant as a treatment for Parkinson's disease. *Expert opinion on investigational drugs*. 2014; 23:1165–1179. [PubMed: 24960254]
11. Emmitte KA. mGlu 5 negative allosteric modulators: a patent review (2010–2012). *Expert Opin Ther Pat*. 2013; 23
12. Ametamey SM, Kessler LJ, Honer M, Wyss MT, Buck A, Hintermann S, et al. Radiosynthesis and preclinical evaluation of 11C-ABP688 as a probe for imaging the metabotropic glutamate receptor subtype 5. *Journal of nuclear medicine*. 2006; 47:698–705. [PubMed: 16595505]
13. Esterlis I, Holmes SE, Sharma P, Krystal JH, DeLorenzo C. Metabotropic Glutamatergic Receptor 5 and Stress Disorders: Knowledge Gained From Receptor Imaging Studies. *Biol Psychiatry*. 2017; doi: 10.1016/j.biopsych.2017.08.25
14. Pillai RLI, Tipre DN. Metabotropic glutamate receptor 5 – a promising target in drug development and neuroimaging. *European Journal of Nuclear Medicine and Molecular Imaging*. 2016; 43:1151–1170. [PubMed: 26743895]
15. Terbeck S, Akkus F, Chesterman LP, Hasler G. The role of metabotropic glutamate receptor 5 in the pathogenesis of mood disorders and addiction: combining preclinical evidence with human Positron Emission Tomography (PET) studies. *Frontiers in Neuroscience*. 2015; 9:86. [PubMed: 25852460]
16. Ametamey SM, Treyer V, Streffer J, Wyss MT, Schmidt M, Blagoev M, et al. Human PET studies of metabotropic glutamate receptor subtype 5 with 11C-ABP688. *Journal of Nuclear Medicine*. 2007; 48:247–252. [PubMed: 17268022]

17. Zhang K, Zhu Y, Zhu Y, Wu S, Liu H, Zhang W, et al. Molecular, Functional, and Structural Imaging of Major Depressive Disorder. *Neuroscience Bulletin*. 2016; 32:273–285. [PubMed: 27142698]
18. Ortega LA, Solano JL, Torres C, Papini MR. Reward loss and addiction: Opportunities for cross-pollination. *Pharmacology, biochemistry, and behavior*. 2017; 154:39–52.
19. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: An emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology*. 2012; 62:63–77. [PubMed: 21827775]
20. Gass JT, Foster Olive M. Glutamatergic substrates of drug addiction and alcoholism. *Biochemical pharmacology*. 2008; 75:218–265. [PubMed: 17706608]
21. Schoepp DD. Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. *Journal of Pharmacology and Experimental Therapeutics*. 2001; 299:12–20. [PubMed: 11561058]
22. Awad H, Hubert GW, Smith Y, Levey AI, Conn PJ. Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus. *J Neurosci*. 2000; 20:7871–7879. [PubMed: 11050106]
23. Attucci S, Carla V, Mannaioni G, Moroni F. Activation of type 5 metabotropic glutamate receptors enhances NMDA responses in mice cortical wedges. *British journal of pharmacology*. 2001; 132:799–806. [PubMed: 11181420]
24. Piers TM, Kim DH, Kim BC, Regan P, Whitcomb DJ, Cho K. Translational concepts of mGluR5 in synaptic diseases of the brain. *Frontiers in pharmacology*. 2012; 3:199. [PubMed: 23205012]
25. Mathew SJ, Shah A, Lapidus K, Clark C, Jarun N, Ostermeyer B, et al. Ketamine for Treatment-Resistant Unipolar Depression: Current Evidence. *CNS drugs*. 2012; 26:189–204. [PubMed: 22303887]
26. Esterlis I, DellaGioia N, Pietrzak RH, Matuskey D, Nabulsi N, Abdallah CG, et al. Ketamine-induced reduction in mGluR5 availability is associated with an antidepressant response: an [11C]ABP688 and PET imaging study in depression. *Mol Psychiatry*. 2017; doi: 10.1038/mp.2017.58
27. D'Souza MS. Glutamatergic transmission in drug reward: implications for drug addiction. *Frontiers in Neuroscience*. 2015; 9:404. [PubMed: 26594139]
28. Mathews DC, Henter ID, Zarate CA. Targeting the Glutamatergic System to Treat Major Depressive Disorder: Rationale and Progress to Date. *Drugs*. 2012; 72:1313–1333. [PubMed: 22731961]
29. Deschwanden A, Karolewicz B, Feyissa AM, Treyer V, Ametamey SM, Johayem A, et al. Reduced metabotropic glutamate receptor 5 density in major depression determined by [11C] ABP688 PET and postmortem study. *The American journal of psychiatry*. 2011; 168(7):727–734. [PubMed: 21498461]
30. Akkus F, Ametamey SM, Treyer V, Burger C, Johayem A, Umbricht D, et al. Marked global reduction in mGluR5 receptor binding in smokers and ex-smokers determined by [11C]ABP688 positron emission tomography. *Proc Natl Acad Sci U S A*. 2013; 110:737–742. [PubMed: 23248277]
31. Akkus F, Treyer V, Johayem A, Ametamey SM, Mancilla BG, Sovago J, et al. Association of Long-Term Nicotine Abstinence With Normal Metabotropic Glutamate Receptor-5 Binding. *Biol Psychiatry*. 2016; 79:474–480. [PubMed: 25861697]
32. Mansvelder HD, McGehee DS. Cellular and synaptic mechanisms of nicotine addiction. *Journal of neurobiology*. 2002; 53:606–617. [PubMed: 12436424]
33. Domin H, Szewczyk B, Wozniak M, Wawrzak-Wlecial A, Smialowska M. Antidepressant-like effect of the mGluR5 antagonist MTEP in an astroglial degeneration model of depression. *Behav Brain Res*. 2014; 273:23–33. [PubMed: 25043733]
34. Palucha A, Branski P, Szewczyk B, Wieronska JM, Klak K, Pilc A. Potential antidepressant-like effect of MTEP, a potent and highly selective mGluR5 antagonist. *Pharmacology, biochemistry, and behavior*. 2005; 81:901–906.

35. Li X, Need AB, Baez M, Witkin JM. Metabotropic glutamate 5 receptor antagonism is associated with antidepressant-like effects in mice. *The Journal of pharmacology and experimental therapeutics*. 2006; 319:254–259. [PubMed: 16803860]
36. Shin S, Kwon O, Kang JI, Kwon S, Oh S, Choi J, et al. mGluR5 in the nucleus accumbens is critical for promoting resilience to chronic stress. *Nat Neurosci*. 2015; 18:1017–1024. [PubMed: 26005851]
37. Wieronska JM, Szewczyk B, Branski P, Palucha A, Pilc A. Antidepressant-like effect of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist in the olfactory bulbectomized rats. *Amino acids*. 2002; 23:213–216. [PubMed: 12373540]
38. Yap JJ, Covington HE 3rd, Gale MC, Datta R, Miczek KA. Behavioral sensitization due to social defeat stress in mice: antagonism at mGluR5 and NMDA receptors. *Psychopharmacology (Berl)*. 2005; 179:230–239. [PubMed: 15517195]
39. Lindemann L, Porter RH, Scharf SH, Kuennecke B, Bruns A, von Kienlin M, et al. Pharmacology of Basimglurant (RO4917523, RG7090), a Unique Metabotropic Glutamate Receptor 5 Negative Allosteric Modulator in Clinical Development for Depression. *Journal of Pharmacology and Experimental Therapeutics*. 2015; 353:213–233. [PubMed: 25665805]
40. Lindemann L, Porter RH, Scharf SH, Kuennecke B, Bruns A, von Kienlin M, et al. Pharmacology of basimglurant (RO4917523, RG7090), a unique metabotropic glutamate receptor 5 negative allosteric modulator in clinical development for depression. *The Journal of pharmacology and experimental therapeutics*. 2015; 353:213–233. [PubMed: 25665805]
41. Geyer, MA., Markou, A. The role of preclinical models in the development of psychotropic drugs. In: Bloom, FE., Kupfer, DJ., editors. *Psychopharmacology: The Fifth Generation of Progress*. Raven Press; New York: 2002. p. 445-455.(2000)
42. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006; 63:856–864. [PubMed: 16894061]
43. Li N, Lee B, Liu R-J, Banasr M, Dwyer JM, Iwata M, et al. mTOR-Dependent Synapse Formation Underlies the Rapid Antidepressant Effects of NMDA Antagonists. *Science*. 2010; 329:959–964. [PubMed: 20724638]
44. Popp S, Behl B, Joshi JJ, Lanz TA, Spedding M, Schenker E, et al. In search of the mechanisms of ketamine's antidepressant effects: How robust is the evidence behind the mTor activation hypothesis. *F1000Research*. 2016; 5:634.
45. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature*. 2016; 533:481–486. [PubMed: 27144355]
46. Cao L, Tian Y, Jiang Y, Zhang GJ, Lei H, Di ZL. Down-Regulation of Homer1b/c Protects Against Chemically Induced Seizures Through Inhibition of mTOR Signaling. *Cellular Physiology and Biochemistry*. 2015; 35:1633–1642. [PubMed: 25824461]
47. Pałucha-Poniewiera A, Szewczyk B, Pilc A. Activation of the mTOR signaling pathway in the antidepressant-like activity of the mGlu5 antagonist MTEP and the mGlu7 agonist AMN082 in the FST in rats. *Neuropharmacology*. 2014; 82:59–68. [PubMed: 24631968]
48. Iijima M, Fukumoto K, Chaki S. Acute and sustained effects of a metabotropic glutamate 5 receptor antagonist in the novelty-suppressed feeding test. *Behav Brain Res*. 2012; 235:287–292. [PubMed: 22921929]
49. Xiao M-Y, Zhou Q, Nicoll RA. Metabotropic glutamate receptor activation causes a rapid redistribution of AMPA receptors. *Neuropharmacology*. 2001; 41:664–671. [PubMed: 11640920]
50. Pomierny-Chamiolo L, Poleszak E, Pilc A, Nowak G. NMDA but not AMPA glutamatergic receptors are involved in the antidepressant-like activity of MTEP during the forced swim test in mice. *Pharmacological reports*. 2010; 62:1186–1190. [PubMed: 21273676]
51. Fukumoto K, Chaki S. Involvement of serotonergic system in the effect of a metabotropic glutamate 5 receptor antagonist in the novelty-suppressed feeding test. *Journal of pharmacological sciences*. 2015; 127:57–61. [PubMed: 25704019]
52. Zhou W, Wang N, Yang C, Li XM, Zhou ZQ, Yang JJ. Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus

- and prefrontal cortex. *European psychiatry : the journal of the Association of European Psychiatrists*. 2014; 29:419–423. [PubMed: 24321772]
53. Quiroz JA, Tamburri P, Deptula D, et al. Efficacy and safety of basimglurant as adjunctive therapy for major depression: A randomized clinical trial. *JAMA Psychiatry*. 2016; 73:675–684. [PubMed: 27304433]
 54. Kågedal M, Cselényi Z, Nyberg S, Raboisson P, Ståhle L, Stenkrona P, et al. A positron emission tomography study in healthy volunteers to estimate mGluR5 receptor occupancy of AZD2066—estimating occupancy in the absence of a reference region. *Neuroimage*. 2013; 82:160–169. [PubMed: 23668965]
 55. De Biasi M, Dani JA. Reward, addiction, withdrawal to nicotine. *Annual review of neuroscience*. 2011; 34:105–130.
 56. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *The American journal of psychiatry*. 2005; 162:1403–1413. [PubMed: 16055761]
 57. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. *Trends in Neurosciences*. 2012; 35:68–77. [PubMed: 22177980]
 58. D'Souza MS, Markou A. The “Stop” and “Go” of Nicotine Dependence: Role of GABA and Glutamate. *Cold Spring Harbor Perspectives in Medicine*. 2013; 3:a012146. [PubMed: 23732855]
 59. D'Souza MS, Markou A. Neuronal Mechanisms Underlying Development of Nicotine Dependence: Implications for Novel Smoking-Cessation Treatments. *Addiction Science & Clinical Practice*. 2011; 6:4–16. [PubMed: 22003417]
 60. D'Souza MS, Markou A. Metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) microinfusions into the nucleus accumbens shell or ventral tegmental area attenuate the reinforcing effects of nicotine in rats. *Neuropharmacology*. 2011; 61:1399–1405. [PubMed: 21896278]
 61. Yararbas G, Keser A, Kanit L, Pogun S. Nicotine-induced conditioned place preference in rats: sex differences and the role of mGluR5 receptors. *Neuropharmacology*. 2010; 58:374–382. [PubMed: 19833142]
 62. Paterson N, Markou A. The metabotropic glutamate receptor 5 antagonist MPEP decreased break points for nicotine, cocaine and food in rats. *Psychopharmacology*. 2005; 179:255–261. [PubMed: 15619120]
 63. Paterson NE, Semenova S, Gasparini F, Markou A. The mGluR5 antagonist MPEP decreased nicotine self-administration in rats and mice. *Psychopharmacology (Berl)*. 2003; 167:257–264. [PubMed: 12682710]
 64. Bespalov AY, Dravolina OA, Sukhanov I, Zakharova E, Blokhina E, Zvartau E, et al. Metabotropic glutamate receptor (mGluR5) antagonist MPEP attenuated cue- and schedule-induced reinstatement of nicotine self-administration behavior in rats. *Neuropharmacology*. 2005; 49(Suppl 1):167–178. [PubMed: 16023685]
 65. Liechti ME, Markou A. Interactive effects of the mGlu5 receptor antagonist MPEP and the mGlu2/3 receptor antagonist LY341495 on nicotine self-administration and reward deficits associated with nicotine withdrawal in rats. *Eur J Pharmacol*. 2007; 554:164–174. [PubMed: 17113075]
 66. Palmatier MI, Liu X, Donny EC, Caggiula AR, Sved AF. Metabotropic Glutamate 5 Receptor (mGluR5) Antagonists Decrease Nicotine Seeking, But Do Not Affect the Reinforcement Enhancing Effects of Nicotine. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2008; 33:2139–2147. [PubMed: 18046312]
 67. Epping-Jordan MP, Watkins SS, Koob GF, Markou A. Dramatic decreases in brain reward function during nicotine withdrawal. *Nature*. 1998; 393:76–79. [PubMed: 9590692]
 68. Der-Avakian A, D'Souza MS, Potter DN, Chartoff EH, Carlezon WA Jr, Pizzagalli DA, et al. Social defeat disrupts reward learning and potentiates striatal nociceptin/orphanin FQ mRNA in rats. *Psychopharmacology (Berl)*. 2017; 234:1603–1614. [PubMed: 28280884]
 69. Der-Avakian A, Mazei-Robison MS, Kesby JP, Nestler EJ, Markou A. Enduring Deficits in Brain Reward Function after Chronic Social Defeat in Rats: Susceptibility, Resilience, and Antidepressant Response. *Biol Psychiatry*. 2014; 76(7):542–549. [PubMed: 24576687]

70. Ramaker MJ, Dulawa SC. Identifying fast-onset antidepressants using rodent models. *Mol Psychiatry*. 2017; 22:656–665. [PubMed: 28322276]
71. Liechti ME, Markou A. Interactive effects of the mGlu5 receptor antagonist MPEP and the mGlu2/3 receptor antagonist LY341495 on nicotine self-administration and reward deficits associated with nicotine withdrawal in rats. *European journal of pharmacology*. 2007; 554:164–174. [PubMed: 17113075]
72. Stoker AK, Olivier B, Markou A. Involvement of metabotropic glutamate receptor 5 in brain reward deficits associated with cocaine and nicotine withdrawal and somatic signs of nicotine withdrawal. *Psychopharmacology*. 2012; 221:317–327. [PubMed: 22147259]
73. Nordquist RE, Steckler T, Wettstein JG, Mackie C, Spooren W. Metabotropic glutamate receptor modulation, translational methods, and biomarkers: relationships with anxiety. *Psychopharmacology*. 2008; 199:389–402. [PubMed: 18322676]
74. Abou Farha K, Bruggeman R, Balj, #xe9, -Volkers C. Metabotropic Glutamate Receptor 5 Negative Modulation in Phase I Clinical Trial: Potential Impact of Circadian Rhythm on the Neuropsychiatric Adverse Reactions; Do Hallucinations Matter? *ISRN Psychiatry*. 2014; 2014:8.
75. Palanisamy GS, Marcek JM, Cappon GD, Whritenour J, Shaffer CL, Brady JT, et al. Drug-induced Skin Lesions in Cynomolgus Macaques Treated with Metabotropic Glutamate Receptor 5 (mGluR5) Negative Allosteric Modulators. *Toxicologic Pathology*. 2015; 43:995–1003. [PubMed: 26059827]
76. Kumar R, Hauser RA, Mostillo J, Dronamraju N, Graf A, Merschhemke M, et al. Mavoglurant (AFQ056) in combination with increased levodopa dosages in Parkinson's disease patients. *The International journal of neuroscience*. 2016; 126:20–24. [PubMed: 24007304]
77. Hughes ZA, Neal SJ, Smith DL, Sukoff Rizzo SJ, Pulicicchio CM, Lotarski S, et al. Negative allosteric modulation of metabotropic glutamate receptor 5 results in broad spectrum activity relevant to treatment resistant depression. *Neuropharmacology*. 2013; 66:202–214. [PubMed: 22551786]
78. Lee KW, Westin L, Kim J, Chang JC, Oh YS, Amreen B, et al. Alteration by p11 of mGluR5 localization regulates depression-like behaviors. *Mol Psychiatry*. 2015; 20:1546–1556. [PubMed: 26370144]
79. Elmenhorst D, Mertens K, Kroll T, Oskamp A, Ermert J, Elmenhorst EM, et al. Circadian variation of metabotropic glutamate receptor 5 availability in the rat brain. *Journal of sleep research*. 2016; 25:754–761. [PubMed: 27357735]
80. DeLorenzo C, Gallezot JD, Gardus J, Yang J, Planeta B, Nabulsi N, et al. In vivo variation in same-day estimates of metabotropic glutamate receptor subtype 5 binding using [(11)C]ABP688 and [(18)F]FPEB. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2017; 37:2716–2727.
81. Insel TR, Cuthbert BN. Endophenotypes: Bridging Genomic Complexity and Disorder Heterogeneity. *Biol Psychiatry*. 2009; 66:988–989. [PubMed: 19900610]
82. Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *Journal of psychiatric research*. 2008; 43:76–87. [PubMed: 18433774]
83. Pergadia ML, Der-Avakian A, D'Souza MS, Madden PA, Heath AC, Shiffman S, et al. Association Between Nicotine Withdrawal and Reward Responsiveness in Humans and Rats. *JAMA psychiatry*. 2014; 71(11):1238–1245. [PubMed: 25208057]
84. Der-Avakian A, Dsouza MS, Pizzagalli DA, Markou A. Bidirectional changes in reward responsiveness during nicotine withdrawal and acute nicotine administration assessed in the response bias probabilistic reward task in rats. *Drug and alcohol dependence*. 2014; 140:e49.
85. Dunlop BW, Betancourt Y, Binder EB, Heim C, Holsboer F, Ising M, et al. Tolerability of the dexamethasone-corticotropin releasing hormone test in major depressive disorder. *J Psychiatr Res*. 2011; 45:24–28. [PubMed: 20488460]
86. Zhukov DA, Vinogradova KP. Learned helplessness or learned inactivity after inescapable stress? Interpretation depends on coping styles. *Integrative physiological and behavioral science*. 2002; 37:35–43. [PubMed: 12069363]

87. Pignatelli M, Vollmayr B, Richter SH, Middei S, Matrisciano F, Molinaro G, et al. Enhanced mGlu5-receptor dependent long-term depression at the Schaffer collateral-CA1 synapse of congenitally learned helpless rats. *Neuropharmacology*. 2013; 66:339–347. [PubMed: 22709946]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript