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A Randomized Trial of a Low Trapping Non-Selective *N*-methyl-D-aspartate (NMDA) Channel Blocker in Major Depression

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Abstract

Background—The high-affinity *N*-methyl-D-aspartate (NMDA) antagonist ketamine exerts rapid antidepressant effects, but has psychotomimetic properties. AZD6765 is a low-trapping NMDA channel blocker with low rates of associated psychotomimetic effects. This study investigated whether AZD6765 could produce rapid antidepressant effects in subjects with treatment-resistant major depressive disorder (MDD).

Methods—In this double-blind, randomized, crossover, placebo-controlled study, 22 subjects with DSM-IV treatment-resistant MDD received a single infusion of either AZD6765 (150 mg) or placebo on two test days one week apart. The primary outcome measure was the Montgomery-Asberg Depression Rating Scale (MADRS), which was used to rate overall depressive symptoms at baseline; at 60, 80, 110, and 230 minutes post-infusion; and on Days 1, 2, 3, and 7 post-infusion. Several secondary outcome measures were also used, including the Hamilton Depression Rating Scale (HDRS).

Results—Within 80 minutes, MADRS scores significantly improved in subjects receiving AZD6765 compared to placebo; this improvement remained significant only through 110 minutes (d=0.40). On the HDRS, a drug difference was found at 80 and 110 minutes and at Day 2 (d=0.49). Overall, 32% of subjects responded to AZD6765 and 15% responded to placebo at some point during the trial. No difference was observed between the groups with regard to psychotomimetic or dissociative adverse effects.

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Supplemental Information: Supplemental Methods, Results, 2 Figures, 1 Table

Conclusions—In patients with treatment-resistant MDD, a single intravenous dose of the low trapping NMDA channel blockerAZD6765 was associated with rapid but short-lived antidepressant effects; no psychotomimetic effects were observed.

Keywords

antidepressant; depression; glutamate; low-trapping NMDA; rapid-acting; treatment-resistant

Introduction

The high potency *N*-methyl-D-aspartate (NMDA) antagonist ketamine has convincingly been demonstrated to exert rapid antidepressant effects within a few hours (1–5). This finding has been replicated in both major depressive disorder (MDD) and bipolar depression and is in stark contrast with the delayed onset associated with currently available antidepressants. These studies have led to a paradigm shift and raised the bar in drug development for depression; as a field, the focus has shifted to developing treatments that significantly improve depressive symptoms in hours instead of weeks (6, 7). By eliminating this delay in therapeutic action, it is anticipated that such compounds, when introduced into the clinic, will dramatically reduce the disruption to personal, family, and social life typical of mood disorders, as well as the risk of suicidal behavior (6).

Nevertheless, ketamine produces psychotomimetic and dissociative side effects. Studies are underway to find safe ways to administer ketamine and to maintain its response in patients with severe depression (8). Presently, however, a critical need remains for new, well-tolerated treatments that act more rapidly than those currently available. One particularly promising pathway for developing rapid-acting antidepressants without psychotomimetic effects is exploring different ways to modulate the NMDA receptor complex. This could be achieved by using low-affinity or NMDA subunit selective receptor antagonists, or by modulating NMDA allosteric sites (9).

The NMDA receptors are tetrameric proteins comprising NR1, NR2, and NR3 subunits; four different NR2 subunits (NR2A-D) exist in the brain. Notably, the NR2B subunit—localized primarily in the forebrain—is a prime target for the development of novel antidepressants. For instance, significantly reduced levels of NR2A and NR2B subunit expression were found in the prefrontal cortex of patients with MDD relative to controls (10). One preclinical study showed that NR2A tyrosine phosphorylation at Tyr 1325 was key to depression-related behaviors in the tail suspension and forced swim tests (11). In preclinical rodent studies, the selective NR2B antagonist Ro25-6981 had significant antidepressant-like properties (12, 13), and was also found to activate the mammalian Target of Rapamycin (mTOR)—a protein linked to ketamine's antidepressant effects (13).

In a double-blind, randomized, placebo-controlled, add-on trial, Preskorn and colleagues tested the NR2B subunit selective NMDA receptor antagonist CP-101,606 in patients with treatment-resistant MDD. A single infusion of CP-101,606 had significant antidepressant effects by Day 5. Dissociative effects were modest and resolved within eight hours, but ceased when the drug dose was reduced (14). Another, small, randomized, double-blind, placebo-controlled, crossover pilot study similarly found that daily doses of an oral formulation of the selective NR2B antagonist MK-0657 (4–8 mg/day) had significant antidepressant effects on secondary efficacy measures as early as Day 5 (15).

AZD6765 is an intravenously-administered, moderate-affinity NMDA receptor channel blocker with almost 100 times less affinity for the channel than the high-affinity NMDA antagonist compound MK801. AZD6765 displaces [^{3}H]MK801 from the NMDA channel with Ki values ranging from 0.56 to 1.48 μM, similar to ketamine which has a Ki value of

0.76 μM. Mealing and colleagues (16) noted a correlation between the degree of trapping and therapeutic safety margin of AZD6765. Trapping channel blockers permit agonist dissociation and channel closure while the antagonist is bound to its site in the channel, whereas partial blockers prevent the channel from closing while blocked (16). Thus it is predicted that the greater the trapping blockade, the greater the risk of psychotomimetic effects. Indeed, ketamine, which induces psychotomimetic effects (17, 18), showed 86% trapping, whereas AZD6765, which has an improved therapeutic safety profile (19, 20), trapped at a much lower level (54% of its initial block). Like ketamine, AZD6765 is also considered a non-selective NMDA channel blocker (21). In animal models of depression, AZD6765 displayed antidepressant-like properties (22). Finally, Phase I studies indicated that AZD6765 had an acceptable safety profile without evidence of psychotomimetic effects up to a dose of 160 mg (23).

Given the need to develop effective glutamatergic modulators with rapid antidepressant effects as well as fewer side effects, this study sought to evaluate the antidepressant efficacy, safety profile, and pharmacokinetics of a single-intravenous infusion of a low-trapping, NMDA channel blocker compared with placebo in subjects with treatment-resistant MDD. We postulated that directly targeting the NMDA receptor with a low-trapping channel blocker would bring about rapid antidepressant effects in patients with MDD. Our primary hypothesis was that a single infusion of AZD6765 would exert a faster and superior antidepressant response than placebo, and that this antidepressant response would occur without psychotomimetic effects. We elected to test a single infusion because this was a proof-of-concept study designed to identify an early antidepressant signal; a positive signal could then warrant further study.

The potential role of serum brain derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and plasma AZD6765 levels were also assessed in conjunction with the antidepressant effects of AZD6765. Chronic administration of antidepressant drugs is known to regulate BDNF serum and tyrosine-related kinase B (trkB) mRNA in rat brain; these interventions could promote neuronal survival and protect neurons from the damage of stress (24). Recent research suggests that serum BDNF concentrations are reduced in individuals with depression, and that successful antidepressant treatment increases serum BDNF concentrations (25). In addition, increased plasma VEGF levels correlated significantly with decreased depression scores in those patients who responded to sleep deprivation, an intervention with rapid antidepressant effects (26).

Methods and Materials

Patient Selection

Subjects were recruited from local inpatient psychiatric units, the internet, and local and national physician referrals. Eligible participants were male and female inpatients, 18 to 65 years old, with a diagnosis of MDD, currently depressed without psychotic features, as diagnosed by the Structured Clinical Interview for Axis I DSM-IV Disorders—Patient Version (SCID-P) (27). Subjects were studied at the National Institute of Mental Health (NIMH) Mood Disorders Research Unit in Bethesda, Maryland, from December 2009 to December 2011. Subjects were required to have a score of ≥20 on the Montgomery-Asberg Depression Rating Scale (MADRS) at screening and at the start of each infusion. Patients were also required to be currently experiencing a major depressive episode lasting at least four weeks and to have had at least two adequate lifetime antidepressant trials that failed, as assessed by the Antidepressant Treatment History Form (ATHF-modified (28)).

All subjects were in good physical health as determined by medical history, physical exam, blood labs, electrocardiogram (ECG), chest x-ray, urinalysis, and toxicology. Subjects were

free from comorbid substance abuse or dependence for at least three months, and judged clinically not to be at serious risk for suicide. Comorbid Axis I diagnoses of anxiety disorders were permitted if they were not the primary focus of treatment within 12 months before screening. Additional exclusion criteria included any serious unstable medical disorder or condition, or concomitant treatment with psychotropic medications in the two weeks before randomization (five weeks for fluoxetine); in addition, female subjects could not be pregnant or nursing. Table 1 lists the demographic and clinical characteristics of the study subjects, and Table 2 describes their current and past medication use.

The study was approved by the Combined Neuroscience IRB at the National Institutes of Health (NIH). All subjects provided written informed consent before entry into the study and were assigned a Clinical Research Advocate from the NIMH Subjects Protection Unit to monitor the consent process and research participation throughout the study.

Conservative estimates of expected change in depressive symptoms in response to AZD6765 were based on previous studies of individuals with MDD; thus, a sample size of 20 was initially expected to reach 81% power with a two-tailed test.

Study design

This was a single center, double-blind, randomized, crossover, placebo-controlled study conducted to assess the efficacy and safety of a single intravenous infusion of the low-trapping NMDA channel blocker AZD6765 in the treatment of MDD. During the study, subjects were not allowed to receive any other psychotropic medications (including benzodiazepines) or to receive structured psychotherapy. Vital signs were monitored during the infusion and for one hour post-infusion. ECG, complete blood counts (CBC), electrolyte panels, and liver function tests were obtained at baseline and at the end of the study.

Following a two-week drug-free period, subjects received intravenous infusions of saline solution and 150 mg of AZD6765 one week apart using a randomized, double-blind, crossover design. The dose of AZD6765 used in the present study was based on previous data indicating that doses up to 160 mg were well tolerated in healthy volunteers. Thus we used 150 mg.

Patients were assigned to receive the two infusions via a random numbers chart. Study solutions were supplied in identical 45-ml syringes containing either 0.9% of saline or 150 mg of AZD6765, which forms a clear solution when dissolved in 0.9 percent saline. The infusions were administered over 60 minutes via a MedFusion 3500 syringe pump on the research unit. All staff were blind to whether drug or placebo was being administered.

Outcome Measures

Subjects were rated 60 minutes prior to the infusion and at 60, 80, 110, and 230 minutes as well as at Days 1, 2, 3, and 7 post-infusion. The MADRS was the primary outcome measure. Secondary outcome measures were: the 17-item Hamilton Depression Rating Scale (HDRS) (29), the Beck Depression Inventory (BDI) (30), the Visual Analogue Scale (VAS) (31), the Hamilton Anxiety Rating Scale (HAM-A) (32), the Scale for Suicide Ideation (SSI) (33), the Brief Psychiatric Rating Scale (BPRS) (34), the Clinician Administered Dissociative States Scale (CADSS) (35), and the Young Mania Rating Scale (YMRS) (36). Ratings for symptoms that could not change over brief periods of time (e.g., sleep, appetite) were carried forward from the initial ratings for those time points. The HAM-A was obtained at al l time points except for minutes 60, 80, and 110. Patient ratings were performed by research nurses or psychologists who trained together to establish reliability. High inter-rater reliability was obtained for the MADRS (ICC = .82), HDRS (ICC=.91), and YMRS (ICC=. 90). Throughout the study, the same rater conducted most ratings for an individual patient.

AZD6765 Plasma Levels

AZD6765 plasma levels were obtained at 60, 80, 110, and 230 minutes post-infusion (see Supplemental Information for methods).

BDNF and VEGF

Serum samples for BDNF and VEGF analysis were collected as putative biomarkers of drug effects. Samples were collected at baseline and at the same time points as rating scales for each of the two study phases. Experiments were carried out in duplicate, and blind to clinical information (see Supplemental Information for methods).

Statistics

Linear mixed models with restricted maximum likelihood estimation were used to examine the fixed, within-subjects effects of time, drug, and a time by drug interaction for each measure. The phase specific baseline was used as a covariate in the intent-to-treat analysis. Schwarz's Bayesian criteria were used to determine the best fitting variance-covariance structure that was compound symmetry. Bonferroni-adjusted simple effects tests were used to examine the location of differences with significant omnibus effects. Cohen's d was calculated for drug differences at specific time points; positive values indicate lower scores on active drug and negative values indicate lower scores on placebo. Significance was evaluated at $p<.05$, two-tailed. Significance levels are reported prior to correction with the exception of post-hoc tests.

Response was defined as a 50% improvement from baseline, and remission was defined as a MADRS score less than 10. Clinicians and patients guessed the drug received in each phase. A McNemar test was used at each time point to compare group response and remission rates as well as the proportion of guesses of active drug on Day 1.

Active drug levels were examined with a linear mixed model including time and a categorical drug response variable. Vital signs, VEGF, and BDNF were examined with mixed models including drug and time effects. EKG and laboratory values were examined with paired *t*-tests comparing pre-study and post-study values in order to determine whether changes occurred over the course of the full study.

Results

Twenty-two patients were randomized to either AZD6765 (150 mg) or placebo before being crossed over to the opposite drug a week later (see Figure S1). Twelve patients received AZD6765 in the first phase and 10 received placebo in the first phase. Twenty-one (95%) patients completed the first phase; one patient dropped out after the first day on AZD6765. A second patient completed the first phase on AZD6765 but did not cross over due to continued improved mood. Thus, 21 of 22 (95%) patients receiving active drug and all (95%) patients receiving placebo completed the corresponding phase. One of the 22 patients mistakenly received one infusion of AZD6765 in 30 minutes; this subject completed both phases and was included in the efficacy and side effect analyses.

Log transformed drug levels were examined in the active phase to determine changes over time and their relation to response. A linear mixed model showed a significant decrease from 60 to 110 minutes post-infusion ($F=4.27$, $df=3,60$, $p=.009$), but antidepressant response did not influence the trajectory (response: $F=0.05$, $df=1,20$, $p=.82$; response x time: $F=0.03$, $df=3,60$, $p=.99$).

Efficacy

A linear mixed model using baseline as a covariate and the MADRS as the outcome showed a significant difference by drug (F=12.10, df=1,299, p<.001), where AZD6765 had lower scores than placebo (d=0.40). The drug by time interaction was not significant (F=1.16, df=7,291, p=.32) (Figure 1).

A factorial repeated measures ANOVA examining baseline MADRS for each phase as well as the order of drugs showed a significant phase effect (F=5.98, df=1,19, p=.02) but no order effect (F=3.60, df=1,19, p=.07) or interaction between phase and order (F=0.18, df=1,19, p=.68). The use of baseline as a time-dependent covariate in the initial model was an attempt to deal with potential phase and order effects. Nevertheless, another model that added order as a between-subjects factor to the original linear mixed model did not show a significant order effect (F=1.54, df=1,17, p=.23), and the drug effect remained significant (F=12.04, df=1,299, p<.001). The first phase was then examined alone. In this model, the drug effect was not significant (F=1.74, df=1,19, p=.20; d=0.60), but the drug by time interaction was significant (F=2.31, df=7,137, p=.03). Post-hoc tests showed significantly lower MADRS scores at 80 and 110 minutes on active drug.

Overall, 32% (7/22) of patients responded to AZD6765, and 15% (3/20) responded to placebo at some point during the study (Figure 2). All patients reached response criteria for the first time at 60 minutes with the exception of one patient who reached response one day following infusion on active drug. Furthermore, 18% (4/22) of patients reached remission on AZD6765, and 10% (2/20) reached remission on placebo at some point during the study. McNemar tests examining response and remission rates by drug at each time point indicated no differences (p's>.21).

Neither clinicians nor patients correctly guessed active drug or placebo more frequently (p>.05).

Secondary analyses were run on additional rating scales in order to examine the effects of AZD6765 on other symptoms. A linear mixed model using the 17-item HDRS showed a significant difference by drug (F=18.39, df=1,306, p<.001), where individuals receiving AZD6765 had lower scores than those receiving placebo (d=0.49) (see Figure S2). Similar results were found for the 6-item version of the HDRS (Drug: F=28.33, df=1,314, p<.001, d=.60; Drug by Time: F=0.71, df=7,284, p=.66). The drug by time interaction was not significant (F=0.48, df=7,247, p=.85). The patient-rated BDI and HAM-A showed significant drug effects but no interaction (drug X time). The VAS depression and anxiety scores showed no significant differences (drug or interaction) (see Supplemental Information). The HDRS and BDI analyses remained significant after Bonferroni corrections were used to adjust for multiple comparisons in the secondary analysis.

When evaluating individual symptoms on the MADRS, 7 of 10 symptoms were significantly improved on AZD6765 compared with placebo; only reduced sleep, suicidal thoughts, and difficulty concentrating were not significantly improved (see Supplemental Information).

No significant drug effects or interactions were observed when data from the BPRS (Figure 1), YMRS (Figure 1), CADSS (Figure S2) or SSI (see Supplemental Information) were analyzed.

VEGF and BDNF Plasma Levels

A linear mixed model examining plasma VEGF levels showed a significant drug main effect (F=11.91, df=1,217, p<.001) but no drug by time interaction (F=0.71, df=5,211, p=.61). VEGF levels were significantly higher in individuals receiving AZD6765 than placebo (d=.

47). For BDNF, no significant drug main effects were observed for the linear mixed model (F=3.24, df=1,218, p=.07) or for drug by time interaction (F=0.33, df=5,211, p=.89). BDNF levels were not significantly higher in patients receiving AZD6765 than placebo (d=.24).

Adverse Events

No serious adverse events occurred during the study. No differences were noted between treatment groups in the emergence of side effects, ECG, laboratory data, vital signs, or weight (see Supplemental Information and Table S1).

Discussion

This double-blind, placebo-controlled, proof-of-concept study found that a single-intravenous infusion of a low-trapping non-selective NMDA channel blocker in patients with treatment-resistant MDD rapidly (within minutes) improved depressive symptoms without inducing psychotomimetic effects. However, this improvement was transitory. To our knowledge, this is the first report showing rapid antidepressant effects associated with a single infusion of a low-trapping non-selective NMDA channel blocker that did not induce psychotomimetic side effects in patients with treatment-resistant MDD.

More specifically, patient depression scores improved significantly more in patients receiving AZD6765 than in those receiving placebo, and this improvement occurred as early as 80 minutes. This difference was statistically significant for the MADRS, HDRS, BDI, and HAM-A. These findings are particularly noteworthy because a large proportion of study participants had a substantial history of past treatment that was not efficacious. The mean number of past antidepressant trials was seven, and 45% of participants had failed to respond to electroconvulsive therapy (ECT).

The antidepressant effects of AZD6765 were not as robust or sustained as those observed in our previous study of ketamine in patients with treatment-resistant MDD (37). We found 1) a comparable onset of antidepressant effects (80 minutes ketamine vs. 110 minutes with AZD6765), but 2) lower response rates at 80 minutes (27% vs. 52%) and Day 1 (14% vs. 71%), 3) lower remission rates at Day 1 (9% vs. 31%), and 4) shorter duration of antidepressant effects (two days for AZD6765 vs. approximately seven days for ketamine as measured by the HDRS). Several possible explanations exist for these differences in efficacy. One possibility is that euphoria or perceptual disturbances were detected instead of antidepressant effects; however, no differences in YMRS or BPRS positive symptoms score were observed on AZD6765 compared to placebo (Figure 1). Furthermore, four of the "core" depression symptoms (depressed mood, guilt, work interests, and psychic anxiety) that typically suggest the greatest improvement in response to both tricyclic and SSRI antidepressants (38–40) improved significantly more on AZD6765 than placebo. It is possible that efficacy would have been increased at higher doses. We used a dose of 150 mg because it is known to be very well tolerated and would maintain the blind. Finally, the brief duration of antidepressant effects seen in the present study could be due to patients' rapid clearance of the compound. However, in this study, we measured 1134 ng/ml one hour after a dose of 150 mg, which is consistent with previous AstraZeneca studies conducted in normal volunteers; across multiple studies, the average plasma levels at the end of a one-hour infusion of 160 mg AZD6765 in healthy volunteers was 1218 ± 287 ng/ml (AstraZeneca on file). The terminal half-life was 12–14 hours across all studies. Unfortunately, we did not measure drug levels beyond the 230-minute time point, and thus are unable to comment on the relationship between blood levels and response at later time points.

With regard to the duration of antidepressant effects, post-hoc tests suggested that the effects of AZD6765 lasted only 110 minutes as assessed by the MADRS, but longer (two days) when the HDRS was used. These differences could be due to subunit selectivity and trapping blockade. It is also possible that ketamine's metabolites may be involved in its relatively sustained antidepressant effects, perhaps acting on off-site targets; a recent report described active ketamine metabolites that last for up to three days (41). It is also important to note that while trapping blockade or broadness of antagonist effects on the NMDA subunit receptors might be key to the robustness of antidepressant effects, these same properties may be involved in ketamine's dissociative and perceptual side effects. Notably, these side effects were not apparent at the dose of AZD6765 tested.

The finding of increased plasma VEGF levels on AZD6765 is of particular interest. We previously reported that increased plasma VEGF levels correlated significantly with decreased depression scores in patients who responded to sleep deprivation, another intervention with rapid antidepressant effects (26). However, clinical studies to date have been mixed with regard to changes in mRNA and serum VEGF and antidepressant response (42, 43). Future studies are needed to evaluate the link between the neurotrophic factor VEGF and rapid antidepressant response to NMDA antagonists.

These results further support the notion that modulating the NMDA receptor complex could bring about rapid antidepressant effects. A number of studies—both controlled and uncontrolled—suggest that the broad NMDA receptor antagonist ketamine exerts rapid antidepressant effects in MDD (5); however, such effects have also been observed with more selective NMDA subunit receptor antagonists that act on NR2B receptors alone, including CP101, 606 (14) and MK-0657 (15). This study is the first to observe such effects with an agent (AZD6765) that acts on NR2A/2B receptors (mixed).

Preclinical studies have postulated that ketamine's mechanism of action is initially mediated by NMDA antagonism but subsequently involves enhanced α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) throughput (12) and, in turn, activates mTOR (13). This same mechanism has been implicated in the antidepressant effects of the NR2B antagonist Ro256981 (13), but it remains unknown whether enhancing AMPA throughput is necessary for the antidepressant effects of CP101,606, MK-0657, or AZD6765. Other mechanisms that have been implicated in the antidepressant effects of ketamine include inhibition of eukaryotic elongation factor 2 (eEF2) and GSK-3 (44, 45). Whether these targets are also involved in the antidepressant effects of any other NMDA receptor antagonists/channel blockers is presently unknown.

This study had several strengths. Notably, subjects were hospitalized for the entire duration of the study, permitting sufficient time to characterize them, and document the stability of depressive symptoms during their current episode. In addition, the study was randomized and placebo-controlled, and subjects were required to have previous antidepressant trials that failed. In prior studies using ketamine (1, 18, 37, 46), blinding may have been an issue, as patients receiving ketamine often experienced transitory perceptual and dissociative disturbances and blood pressure changes; such features could have compromised the study blind in those studies. In the present study, we tested blinding and asked raters and patients to guess treatment assignment. Neither clinicians nor patients were more likely to correctly guess whether they were receiving study drug or inactive placebo, suggesting that study blind was preserved. In addition, no significant changes in blood pressure were noted between patients receiving AZD6765 and those receiving placebo, another potential issue that could have compromised study blind. Overall, AZD6765 was well tolerated; no side effects were more common with drug than placebo.

Nevertheless, several limitations also exist. First, the group size was small; it is possible that a larger sample size would have revealed additional time points of efficacy. In addition, the subjects in this study were a refractory subgroup of patients with treatment-resistant MDD who had substantial prior treatment (Table 1); thus the results may not be generalizable to patients with MDD who have different illness characteristics. Patients in this study also had high rates of comorbid anxiety disorders (lifetime rates of 55%).

As noted previously, novel, effective, and rapid-acting treatments for MDD are urgently needed. Taken together, the present results support the hypothesis that targeting the NMDA receptor complex brings about rapid antidepressant effects in patients with MDD. The compound tested—AZD6765—had rapid but short-lived antidepressant effects. The findings suggest that the acute improvement in depressive symptoms observed here was not associated with psychotomimetic effects or unblinding of the study. Based on the positive antidepressant signal noted here, future studies with this compound are warranted, particularly those exploring efficacy and tolerability associated with higher or repeated doses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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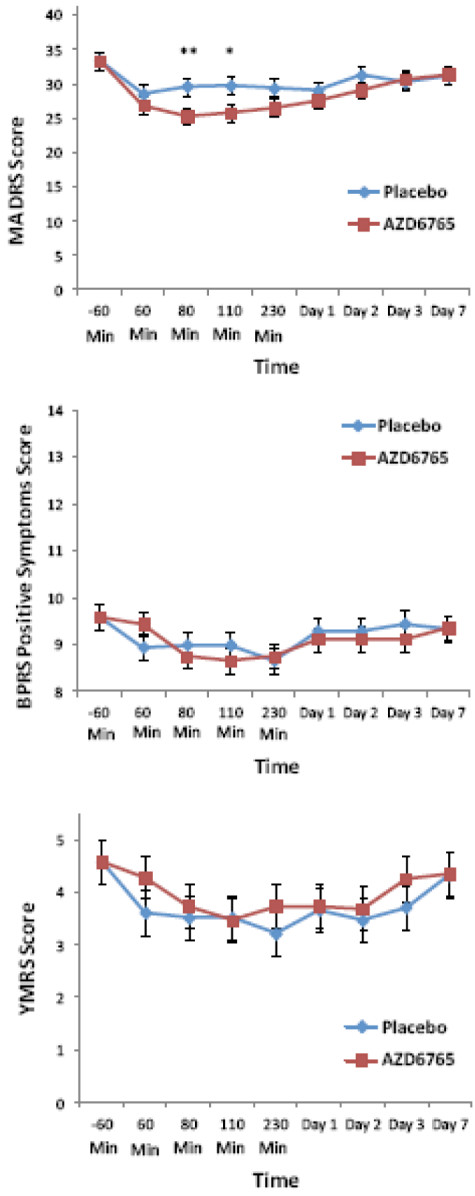

Figure 1.

Change in Montgomery Asberg Depression Rating Scale (MADRS), Brief Psychiatric Rating Scale (BPRS) positive symptom, and Young Mania Rating Scale (YMRS) scores over one week (n=22). Values are expressed as generalized least square means and standard errors for the Intent to Treat (ITT) analysis. *indicates $P<0.05$, ** $P<0.01$, *** $P<0.001$.

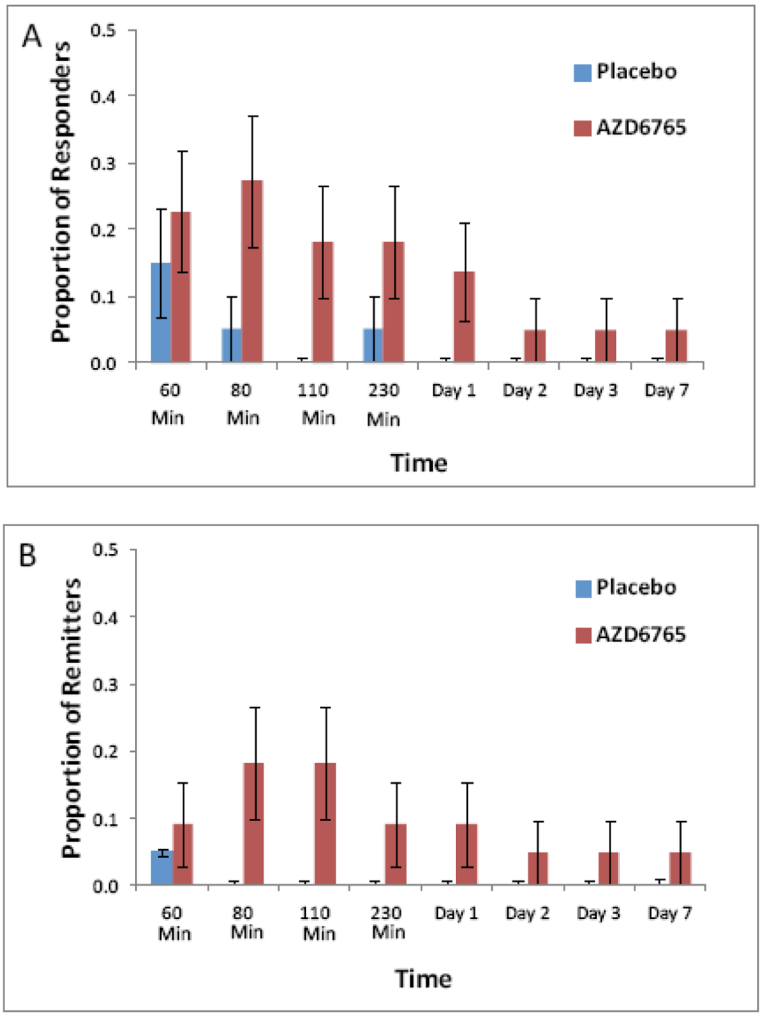

Figure 2.

(A) Proportion of responders (50% improvement on Montgomery Asberg Depression Rating Scale (MADRS)) to AZD6765 and placebo from 60 minutes to Day 7 post-infusion (n=22). **(B)** Proportion of remitters (MADRS <10) on AZD6765 and placebo from 60 minutes to Day 7 post-infusion (n=22).

Table 1

Demographic and Clinical Characteristics of the Patient Sample (n=22)

	Mean	SD
Age (Years)	51.5	10.1
Age of Onset (Years)	23.3	12.9
Length of Illness (Years)	28.6	15.6
Length of Current Episode (Months)	107.9	126.5
Trials		
• Antidepressant		
• Current Episode	3.3	3.3
• Lifetime	6.6	4.0
Body Mass Index	25.9	3.7
	N	%
Sex (Male)	12	55
Education		
• Graduate School	7	32
• College Graduate	9	41
• Some College	5	23
• High School	1	5
Disability	11	50
Unemployed	17	77
Family History		
• Mood Disorder	17	77
• Alcohol Abuse or Dependence	11	50
Lifetime Diagnosis		
• Alcohol Abuse or Dependence	6	27
• Substance Abuse or Dependence	2	9
• Anxiety Disorder	12	55
Suicide Attempt	5	23
Subtype		
• Atypical	5	23
• Melancholic	7	32
• Neither	10	46
2 or More Trials (Current Episode)		
• Antidepressant	14	64
• Psychotropic	16	73

Table 2

Medication use during current major depressive episode and lifetime (N=22)

	Current		Lifetime	
Medication/Treatment*	**N**	**%**	**N**	**%**
Antidepressants				
• SSRI	14	64	21	95
• Venlafaxine	9	41	16	73
• Duloxetine	8	36	15	68
• Bupropion	8	36	14	64
• MAOI	4	18	8	36
• Mirtazapine	3	14	7	32
• TCA	3	14	6	27
• Nefazodone	3	14	3	14
• Trazodone	1	5	2	9
Atypical Antipsychotics	4	18	9	41
• Quetiapine	3	14	5	23
• Aripiprazole	1	5	4	18
• Risperidone	1	5	4	18
• Ziprasidone	1	5	3	14
• Olanzapine	0	0	2	9
Anticonvulsants				
• Lamotrigine	2	9	6	27
• Valproate	2	9	6	27
• Oxcarbazepine	2	9	2	9
• Gabapentin	0	0	3	14
• Topiramate	0	0	1	5
Other				
• Benzodiazepines	7	32	9	41
• Stimulants	5	23	5	23
• Modafinil	2	9	2	9
• Desvenlafaxine	4	18	4	18
• ECT	3	14	10	45
• Lithium	2	9	7	32
• Hypnotics	2	9	4	18
• Thyroid Augmentation	2	9	3	14
• Amoxapine	1	5	1	5
• Pregabalin	1	5	1	5
• Atomoxetine	0	0	1	5
• Donepezil	0	0	1	5
• Methylphenidate	0	0	1	5
• Pramipexole	0	0	1	5

Abbreviations: ECT, electroconvulsive therapy; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VNS, vagal nerve stimulation.

*Adequate trial based on the Antidepressant Treatment History Form-modified (ATHF-modified), modified to include adequate trial definition for newer antidepressants and pramipexole.