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Letter to the Editor

Riluzole likely lacks antidepressant efficacy in ketamine non-responders

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In our primary analysis of a four-week riluzole extension trial after open-label ketamine in 42 treatment-resistant major depressive disorder (TRD) patients, there was no significant difference in depression scores between riluzole and placebo extension (Ibrahim et al., 2012). Riluzole also did not delay relapse in ketamine responders, which is consistent with a prior report of lack of efficacy in 14 ketamine responders (Mathew et al., 2010). However, as riluzole has been proposed to have adjunctive antidepressant effects in TRD (Sanacora et al., 2007; Zarate et al., 2004) and, although glutamatergic, its mechanism of action is distinct from ketamine (Niciu et al., 2012), we hypothesized that riluzole has antidepressant effects in ketamine *non*-responders.

As described previously (Ibrahim et al., 2012), following a 2-week drug-free period (5 weeks for fluoxetine), 52 (10 additional patients were recruited after the primary report) TRD inpatients in a current major depressive episode provided written informed consent for the Combined Neuroscience Institutional Review Board of the National Institutes of Health (NIH)-approved protocol. Treatment resistance was defined as inadequate response to ≥2 adequate antidepressant or device-based (including electroconvulsive therapy) trials. All subjects had at least moderate depression severity [Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score ≥22 at screening and on the day of ketamine infusion with no greater than a 25% decrease between screening and infusion]. All 52 subjects received a single open-label subanesthetic dose (0.5 mg/kg) ketamine infusion over 40 min. 4–6 h post-infusion, subjects were randomized double-blind to either flexible-dose (100–200 mg/day) riluzole or placebo twice daily for four weeks. Dose escalations were allowed on a weekly basis, and dose reductions were permitted by one capsule (50 mg/week to a minimum of 100 mg/day) for intolerable side effects. Subjects were rated with a battery of neuropsychiatric measures at 60 min pre-infusion (baseline), at several post-infusion time points (+40, +80, +120 and +230 min) and daily throughout the next 28 days. Only the MADRS is reported here as change in total score was the primary outcome measure. Factorial linear mixed models with restricted maximum likelihood estimation and an autoregressive moving average covariance structure were used to examine change in clinical ratings with time as a within-subjects factor and drug as a between-subjects factor. MADRS at 230 min (last pre-randomization time point) was included as a covariate. Potential interactions between time and drug were also included in the model. The fixed intercept was included, but the random intercept and random subject effect were not included because they did not contribute significantly to the model. Responders and non-responders were defined as ≥50% and <50% improvement, respectively, from baseline MADRS at 230 min.

As defined, 32 patients were non-responders, and 16 non-responders were randomized to each arm. There were no significant differences in demographic or neuropsychiatric characteristics (including length of illness, length of current major depressive episode and number of failed antidepressant trials) between groups (Supplemental Table 1). The linear mixed model showed no main effect of drug [$F(1,29) = 0.62$, $p = .44$] or time [$F(27,231) = 1.50$, $p = .058$]. There was also no interaction between drug and time [$F(27,231) = 1.15$, $p = .29$] (Fig. 1). This small sample size, however, may leave the study underpowered to detect a small-to-medium effect. In non-responders, riluzole's maximum effect was observed at day one ($d = .39$) but was lost by day six post-infusion (Fig. 1). Yet, at the end of protocol, sample sizes were even smaller due to attrition – placebo: 8/16 (50%) drop-outs; riluzole: 6/16 (38%) drop-outs. There was no statistically significant difference in drop-outs between groups ($p = .72$), and, with the exception of one patient randomized to riluzole who discontinued due to severe nausea, drop-out was attributable to psychiatric indications, *i.e.* continued poor and/or worsening mood, anxiety or suicidal ideation. At day 28, there was only one antidepressant responder randomized to placebo (6%) and no responders randomized to riluzole (drop-outs were counted as non-responders).

Although riluzole has been included in TRD treatment algorithms (Shelton et al., 2010) and hypothesized to have an antidepressant mechanism distinct from ketamine – among proposed effects, riluzole increases synaptic reuptake of glutamate by increasing expression/activity of the astrocytic excitatory amino acid transporter, GLT-1/EAAT2, thereby *decreasing* synaptic glutamate levels (Banasr et al., 2010) – in this small sample, riluzole did not have antidepressant efficacy in ketamine non-responders. There are several potential limitations, however, that may preclude broader generalization. First, our ketamine non-responders are a highly refractory cohort, having failed ≥2 standard antidepressant trials and ketamine, which has a large-to-very large antidepressant effect in TRD (Niciu et al., 2014). As prior studies suggest, riluzole may be more effective in less refractory depression (Sanacora et al., 2007; Zarate et al., 2004); this is currently under investigation in serotonin reuptake inhibitor refractory patients (ClinicalTrials.gov identifier: NCT01204918). Second, in TRD (Zarate et al., 2004) and lithium-treated bipolar

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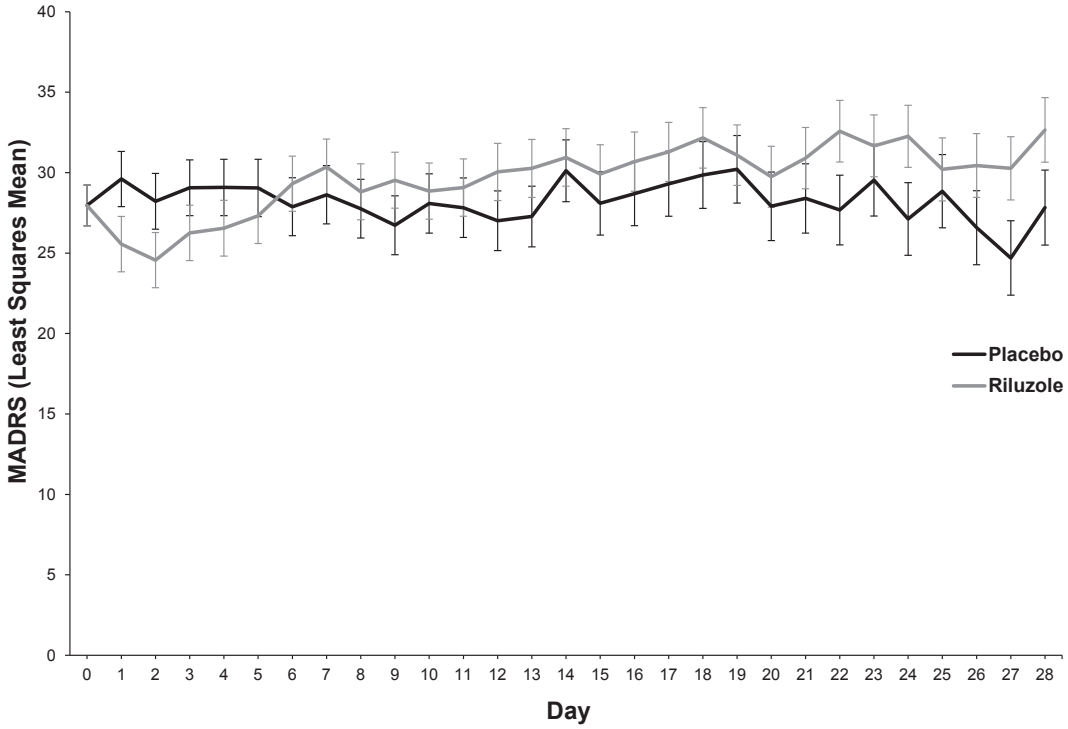

Fig. 1. Riluzole Appears to Lack Antidepressant Efficacy in Ketamine Non-Responders. On randomization to flexible dose riluzole (100–200 mg/day) or placebo 4–6 h after a single open-label subanesthetic dose (0.5 mg/kg) ketamine infusion, there was no difference in antidepressant efficacy over the ensuing four weeks in ketamine non-responders (as defined by <50% MADRS improvement from pre-randomization baseline at 230 min post-infusion) [group × time interaction: [$F(27,231) = 1.15$, $p = .29$], Abbreviations: TRD: treatment-resistant major depressive disorder.

depression (Zarate et al., 2005), riluzole's first significant antidepressant effects were observed at three and five weeks, respectively. Therefore, our 28-day trial might be of insufficient duration to detect an effect over placebo. However, as displayed in Fig. 1, MADRS scores in the riluzole group approached their pre-infusion baseline in the final week of the study, suggesting that these subjects were not on a trajectory towards improvement. In conclusion, although potentially underpowered to detect a small-to-moderate-sized effect, riluzole is unlikely to be an effective antidepressant strategy in ketamine non-responders.

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Contributors

All authors contributed to the conception, data gathering, data analysis, writing and/or revision of this manuscript.

Conflict of interest

Drs. Niciu, Ionescu, Richards, Vande Voort, Ballard, Ms. Brutsche and Mr. Luckenbaugh have no potential financial conflicts of interest to disclose. Dr. Furey is listed as a co-inventor on a patent application for the use of scopolamine in major depression, and Dr. Zarate is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. Drs. Furey and Zarate have assigned their rights in the patent to the U.S. Government but will share a percentage of any royalties that may be received by the Government.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.07.022.

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